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Effect of sildenafil citrate on the cardiovascular system

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Abstract

Sildenafil citrate is a drug commonly used to manage erectile dysfunction. It is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4 ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate ($C_{22}H_{30}N_6O_4S$). It is a highly selective inhibitor of cyclic guanine monophosphate-specific phosphodiesterase type 5. In late March through mid-November 1998, the US Food and Drug Administration (FDA) published a report on 130 confirmed deaths among men (mean age, 64 years) who received prescriptions for sildenafil citrate, a period during which >6 million outpatient prescriptions (representing about 50 million tablets) were dispensed. The US FDA recently reported that significant cardiovascular events, including sudden cardiac death, have occurred in men with erectile dysfunction who were taking sildenafil citrate. These reports have raised concerns that sildenafil citrate may increase the risk of cardiovascular events, particularly fatal arrhythmias, in patients with cardiovascular disease. In the past few years, the cardiac electrophysiological effects of sildenafil citrate have been investigated extensively in both animal and clinical studies. According to extensive data available to date, sildenafil citrate has been shown to pose minimal cardiovascular risks to healthy people taking this drug. Some precautions are needed for patients with cardiovascular diseases. However, the only absolute contraindication for sildenafil citrate is the concurrent use of nitrates. This article is intended to review sildenafil citrate's cardiovascular effects, as well as current debates about its arrhythmogenic effects.

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- Cardioprotection

Introduction

Sildenafil citrate was the first oral drug approved for the treatment of erectile dysfunction (ED), which is frequently observed in men with cardiovascular disease (1). ED is defined as the inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity (2). The prevalence of moderate to complete ED has been reported to be >30% in men aged 40 to 70 years (3). Since the approval of sildenafil citrate, several reports of sudden death among patients treated with this drug have raised some concerns regarding its safety in patients with coronary artery disease (4). In the past few years, the cardiovascular effects of sildenafil citrate have been investigated extensively in both animal and clinical studies. In this article we shall review these studies, as well as

the current debate about sildenafil citrate's arrhythmogenic effects.

Erectile dysfunction and cardiovascular disease

ED is a common health concern among patients with cardiovascular disease. According to the Massachusetts Male Aging Study, 34.8% of men aged 40 to 70 years have moderate to complete ED, and 15% of men aged 70 have complete ED (3). The risk of ED has been shown to markedly increase with age, with a high prevalence of ED found in patients with cardiovascular disease (3). Greenstein and colleagues (5) have shown that there is a significant correlation between the severity of ED and the number of vessels involved in patients with coronary artery disease (CAD). The age-adjusted prevalence of complete ED has been reported to be 1.5 times higher in men with hypertension than in the entire population studied (3). Epidemiologic studies have reported that ED is commonly found in smokers, diabetics and patients with hypercholesterolemia; thus, ED shares important risk factors with CAD (6). A report by Khan and colleagues (7) also found that patients with CAD and peripheral vascular disease have an increased prevalence of ED.

Sildenafil citrate and erectile dysfunction

ED is considered to be a significant medical condition because it can lead to a loss of self-esteem, frustration, depression, and difficulty with disruption of sexual relationships (8). Increasing attention has recently been focused on ED due to the advent of effective oral treatments. Although ED was once diagnosed and treated primarily by urologists, primary care physicians and other specialists such as cardiologists now write ~80% of the prescriptions for sildenafil citrate, the most popular drug used to treat this condition (9).

Sildenafil citrate is a useful tool for the treatment of ED because it selectively inhibits its phosphodiesterase type 5 (PDE-5) (10), which inactivates cyclic guanine monophosphate (cGMP), the mediator of smooth muscle relaxation in the corpus cavernosum. By selectively inhibiting cGMP catabolism in cavernosal smooth-muscle cells (10), sildenafil citrate can restore the natural erectile response to sexual stimulation without causing erections in the absence of such stimulation. Sildenafil citrate is rapidly absorbed, with maximal plasma concentrations occurring within 1 h after oral administration and a mean terminal half-life of 3 to 5 h (10). Sildenafil citrate has been shown to be an effective treatment for ED. However, after sildenafil citrate was approved by the US Food and Drug Administration (FDA) in 1998, several deaths were reported in patients taking sildenafil citrate. It was generally assumed that they were related to an underlying disease (e.g., ischemia) and not to a specific drug effect (11). Nevertheless, these reports raised concerns that sildenafil citrate may increase the risk of cardiovascular events in men with ED and cardiovascular disease (12), which led to many basic and clinical investigations of the adverse cardiovascular effects of this drug (12).

Use of sildenafil citrate in patients with cardiovascular disease

Sildenafil citrate is a cGMP-specific PDE-5 inhibitor (10). PDE-5, which is located primarily in the cavernous body, thrombocytes and vascular smooth muscle cells, degrades cGMP (13). Thus, by inhibiting PDE-5, sildenafil citrate selectively increases cGMP levels (10). It shows far less affinity for other phosphodiesterase isozymes, including PDE-1, which is abundant in ventricular myocytes (14). However, concern about adverse cardiovascular effects remains (15) since PDE-5 inhibitors promote vasodi-

lation, and thus have the potential to cause hypotension. This concern has been greatest for elderly patients with pre-existing cardiovascular disease. Mittleman and colleagues (16) reviewed the clinical database for this drug, which supports its cardiovascular safety in a wide range of patients. During placebo-controlled trials, the rate of myocardial infarction (MI) or cardiovascular death was 0.91 (95% CI: 0.52-1.48) per 100 person-years (PY) of follow-up among sildenafil citrate-treated patients compared with 0.84 (95% CI: 0.39-1.60) per 100 PY of follow-up among placebo-treated patients. The relative risk of MI or cardiovascular death was 1.08 (95% CI: 0.45-2.77) for sildenafil citrate compared with placebo (P = 0.88). During open-label studies, the rate of MI or cardiovascular death was 0.56 (95% CI: 0.44-0.72) per 100 PY of follow-up. This analysis demonstrated that rates of MI and cardiovascular death are low and comparable between men treated with sildenafil and those treated with placebo, suggesting that the use of sildenafil citrate is not associated with an increase in the risk of MI or cardiovascular death (16). Manfroi and colleagues (17) studied male patients who were referred for coronary angiography with a diagnosis of chronic stable angina. Hemodynamic measurements were taken during right and left heart catheterization in the basal state, and 60 min after 50 mg of oral sildenafil. A single oral dose of sildenafil citrate had no significant hemodynamic effects in supine patients with stable angina and, thus, the authors concluded that isolated administration of sildenafil citrate does not appear to be associated with adverse cardiovascular effects (17). The ACC/AHA consensus statement recommended that patients taking sildenafil citrate with combinations of antihypertensive drugs (such as calcium-channel blockers, ß-blockers, diuretics, and angiotensin-converting enzyme inhibitors) be alerted to the possibility of hypotension, particularly patients with congestive heart failure (18). The Princeton Consensus Panel concluded that patients with well-controlled hypertension can be safely managed with approved medical treatments for ED (12). However, concomitant use of nitrates is considered to be an absolute contraindication for the use of sildenafil citrate (19). Nitrates are prescribed in several different forms, including sublingual nitroglycerin, oral isosorbide mononitrate or dinitrate, nitropatch, and nitropaste, all of which have been associated with a prolonged decrease in blood pressure when used concomitantly with sildenafil citrate (19). Nitrates are metabolized in vessel walls, where they release nitric oxide. Sildenafil citrate prolongs the vasodilatory effects of nitrates by decreasing the breakdown of nitric oxide's main effector, cGMP. It is not known how much time must elapse between administration of sildenafil citrate and administration of nitrates to avoid significant hypotensive effects (19), but it has been suggested to assume an interval of at least 24 h (19). Nitroprusside also causes vasodilatation by nonenzymatic release of nitric oxide, and thus is predicted to have a synergistic hypotensive effect with sildenafil citrate (19).

Effects of sildenafil citrate on cardiac contractility, blood pressure and heart rate

Sildenafil citrate belongs to a class of compounds called PDE inhibitors. PDEs comprise a diverse family of enzymes that hydrolyze cyclic nucleotides (cAMP and cGMP) and therefore play a critical role in the modulation of second messenger signaling pathways (13). Sildenafil citrate is a highly selective (~4,000-fold) inhibitor of human PDE-5 over human PDE-3 (19). This is important because inhibitors of PDE-3 (the isozyme involved in the regulation of cardiac contractility), such as milrinone, vesnarinone and enoximone, which have been used in patients with heart failure, are

generally associated with an increased incidence of cardiac arrhythmias and other serious side effects (20). The cardiotoxic effects of PDE-3 inhibitors are thought to be related to an increase in intracellular cAMP in the myocardium (21,22). However, PDE-5 is not present in cardiac myocytes (19). Corbin and colleagues (23) demonstrated in both dog and human hearts that sildenafil citrate was unlikely to directly produce an inotropic effect on cardiac muscle.

Systemic and pulmonary arterial and venous smooth muscle cells contain PDE-5. However, sildenafil citrate causes only a mild and transient decrease in blood pressure (8-10 mmHg for systolic blood pressure and 5-6 mmHg for diastolic blood pressure) (19). The peak effects are evident 1 h after the dose is given and last for approximately 4 h (19). Heart rate and cardiac output are not significantly affected. Along with a mild decrease in systemic vascular resistance and afterload, there is also a mild decrease in preload and stroke volume due to venous vasodilatation. These effects are not dependent upon age or dose (within the range of 25 to 800 mg) (19). In a study of patients with severe coronary artery disease, Herrmann and colleagues (24) confirmed that the hemodynamic effects of sildenafil citrate (when taken alone) are not associated with clinically significant hypotension.

Effects of sildenafil citrate on central hemodynamics and peripheral vasculature

In normal volunteers, no significant changes in cardiac index were evident up to 12 h after administration of oral sildenafil citrate (100 to 200 mg) or intravenous sildenafil citrate (20 to 80 mg) (19). Significant decreases in the systemic vascular resistance index were reported at the end of intravenous sildenafil citrate infusion (20 to 80 mg), when plasma concentrations were highest (19). Sildenafil citrate has both vasodilator and venodilator effects on the peripheral vasculature (19). In 8 patients with stable angina, intravenous sildenafil citrate reduced systemic and pulmonary arterial pressures, as well as cardiac output, by 8, 25, and 7%, respectively, consistent with its mixed arterial (systemic and pulmonary hypotension) and venous (drop in stroke volume secondary to decreased preload) vasodilator effects (25).

Although the therapeutic efficacy of sildenafil citrate in the treatment of ED has been proven, little is known about the potential beneficial effects of sildenafil citrate in other diseases. Studies in rats demonstrated that PDE-5 inhibition with sildenafil attenuates the rise in pulmonary artery pressure and vascular remodeling when given before chronic exposure to hypoxia-induced pulmonary hypertension (26). Likewise, clinical investigations in patients with pulmonary arterial hypertension have shown that sildenafil citrate therapy may be beneficial to patients receiving long-term infusion of epoprostenol (27,28). A recent meta-analysis study has suggested that the validity of the observed effect of sildenafil on pulmonary hypertension is not conclusive due to small participant numbers and inadequate investigation of different disease etiologies. In addition, further studies are needed to investigate the long-term outcome (29).

Sildenafil citrate and sudden cardiac death

Sudden cardiac death is a major cause of death in many industrialized countries including Thailand (27,30). It is most often caused by a lethal cardiac arrhythmia known as ventricular fibrillation (VF) (27,30-35). VF has been characterized as a rapid, disorganized, and asynchronous contraction of ventricular muscle, which causes the failure of the pumping function of the heart, leading to vital organ failure and causing death within minutes (36-39). According to a report by

the World Health Organization, the annual incidence of sudden cardiac death in industrialized countries ranges from 10 to 32% of natural deaths, depending upon the time that elapses from the onset of symptoms to death, making it the most common form of fatal cardiac disease (40). In the past few years, a growing number of studies have reported that this lethal arrhythmia led to sudden cardiac death in many middle-aged men treated with sildenafil citrate (41).

Post-marketing surveillance data after the approval of sildenafil citrate by the US FDA revealed significant cardiovascular problems, including sudden cardiac death, related to the use of sildenafil citrate (4). As of February 1999, the US FDA had received 401 reports of death among men who had received a prescription for sildenafil citrate over the prior 10 to 11 months. These included 219 cardiovascular events (MI, arrhythmia, cardiac arrest, collapse), 140 sudden deaths, and 18 cerebrovascular accidents. The reporting period represented about 4 million to 5 million men and approximately 9 million prescriptions, which translates to approximately 8.5 deaths per million men per month (4). However, it was determined from an analysis of adverse events reported to the FDA between March 1998 and August 1999 that important data were missing from these reports, such as medical histories, cause of death and sildenafil citrate dosing (42).

As of September 30, 2001, Pfizer's clinical safety database contained information on the extent of exposure to sildenafil citrate from 124 completed and ongoing double-blind and open-label clinical trials involving 5054 placebo-treated and 6896 sildenafil citrate-treated patients, representing 2593 PY of observation (43). Analysis of these data revealed that the overall MI incidence rate was similar in placebo-treated (0.95/100 PY) and sildenafil citrate-treated patients (0.85/100 PY; P = 0.801). For the open-label studies, analysis of data from patients representing 10,859 PY of sildenafil citrate exposure demonstrated an MI incidence rate of 0.53/100 PY. The overall MI rate for double-blind and open-label sildenafil citrate-treated patients was 0.58/100 PY. Similar rates have been reported in a number of epidemiologic studies (44). The database also contains (as of September 30, 2001) reports of 5 deaths (from all causes) among double-blind placebo-treated patients and 9 deaths among sildenafil citrate-treated patients. This corresponds to all-cause mortality rates of 0.53/100 PY and 0.55/100 PY, respectively (P = 0.945). The overall (double-blind and open-label) mortality rate among sildenafil citrate-treated patients was 0.37/100 PY, which is lower than that (0.66/100 PY) calculated for men aged 40 to 64 years in the US for 1999. These results clearly show that the incidences of MI and all-cause mortality among patients who received double-blind and/or open-label sildenafil citrate treatment are similar to those observed among patients who received placebo, or in men in the same age cohort of the general population (43). Carson III (45) reported that the incidence of adverse cardiovascular events in patients taking sildenafil does not differ from that for the general population.

Cardiac electrophysiological effects of sildenafil citrate

In the past few years, the cardiac electrophysiological effects of sildenafil citrate have been investigated extensively (46). Geelen and colleagues (46) demonstrated that sildenafil citrate induces a dose-dependent block of the rapid component of the delayed rectifier potassium current (I_{Kr}). They also reported that sildenafil citrate can have an action similar to that of class III antiarrhythmic drugs (46). These effects are observed at concentrations that may be found in conditions of impaired drug elimination such as renal or hepatic insufficiency, during co-administration of another CYP3A4 inhibi-

tor, or after drug overdose (11). Prolonged cardiac repolarization caused by sildenafil citrate could result in malignant ventricular arrhythmias and lead to sudden cardiac death in some of these patients (11). Swissa and colleagues (47) demonstrated that a combination of sildenafil citrate and a nitric oxide donor increases ventricular tachyarrhythmia/VF vulnerability in the normal right ventricle of swine.

Although many reports have demonstrated the arrhythmogenic effects of sildenafil citrate, some studies have reported otherwise. Vardi and colleagues (48) showed that sildenafil citrate does not alter the hemodynamic responses to exercise or change the incidence of ventricular arrhythmias in men with cardiovascular disease and ED. Chiang and colleagues (49) found that sildenafil citrate at concentrations up to 30 µM has no significant effect on either the rapid (I_{Kr}) or the slow (I_{Ks}) components of the delayed rectifier potassium currents in guinea pig ventricular myocytes. They also found that sildenafil citrate dose-dependently blocks L-type Ca^{2+} currents ($I_{Ca,L}$), but has no effect on persistent Na^{+} currents. They concluded that sildenafil citrate does not prolong cardiac repolarization. Instead, in supra-therapeutic concentrations, it accelerates cardiac repolarization, presumably via its blocking effect on $I_{Ca,L}$ (49). Recent studies have also demonstrated that oral administration of 50 mg sildenafil citrate does not affect QT dynamic properties (50). Furthermore, Nagy and colleagues (51) recently reported that sildenafil citrate reduces arrhythmia severity during ischemia 24 h after oral administration in dogs.

Cardioprotective effects of sildenafil citrate

Ischemic preconditioning results in powerful cardioprotective effects (52). Repeated brief episodes of ischemia initiate a cascade of intracellular signaling events which help prevent future myocardial infraction and stunning (52). After initial observation, this phenomenon, termed "myocardial preconditioning", was studied intensively to try to understand its cellular mechanisms and apply this knowledge towards protection of the human heart from ischemic heart disease. Current data suggest that sildenafil citrate has a preconditioning-like cardioprotective effect in the rabbit, rat and mouse heart (53). Das and colleagues (54) reported that sildenafil citrate at a much lower dose (0.05 mg/kg) provides significant cardioprotection in isolated perfused rat hearts following global ischemic-reperfusion. They observed an improved post-ischemic recovery of ventricular function, a reduction in the incidence of VF, and a decrease in MI. At higher doses, sildenafil caused a significant increase in the incidence of VF, while at very low doses it had no effect on cardiac function (54). However, a study by Reffelmann and Kloner (55) demonstrated otherwise. In their report, they did not find a decrease in myocardial necrosis following ischemia-reperfusion in a rabbit model. The reason for these negative results was not clear. The only noticeable difference in the experimental procedure was a considerably longer drug infusion time (~5 min) in the study by Reffelmann and Kloner (55) as compared to that used by Ockaili and colleagues (56) (~1 min), which could potentially affect the hemodynamic response prior to ischemia.

Signaling mechanisms in sildenafil-induced cardioprotection

Although sildenafil citrate has been shown to have a powerful preconditioning-like cardioprotective effects in animal models of ischemia-reperfusion injury, the precise cellular mechanism underlying these effects remains unclear. The sildenafil citrate-induced cardioprotective effect against ischemia-reperfusion injury is dependent upon the opening of mitochondrial ATP-

sensitive potassium channels (mitoK_{ATP} channels) in rabbits (56). It has been proposed that the vasodilatory action of sildenafil citrate could potentially cause the release of endogenous mediators of preconditioning, such as adenosine or bradykinin from endothelial cells, which may trigger a signaling cascade (through the action of kinases) and the release of nitric oxide (56). Generation of nitric oxide could potentially activate guanylate cyclase, resulting in an enhanced formation of cGMP (57). cGMP may activate protein kinase G, which could then open mitoK_{ATP} channels, resulting in both acute and delayed cardioprotective effects (58). Mitochondria are known to play an essential role in cell survival via ATP synthesis and maintenance of Ca^{2+} homeostasis (59). Opening mitoK_{ATP} channels partially compensates the membrane potential, which enables additional protons to be pumped out to form an H^+ electrochemical gradient to drive both ATP synthesis and Ca^{2+} transport. Recently, Das and colleagues (60) reported that protein kinase C also plays an essential role in sildenafil-induced cardioprotection in rabbits.

We conclude that, in view of the increasing incidence of sudden cardiac death in ED patients treated with sildenafil citrate, it is essential to understand how this drug affects the entire cardiovascular system, especially the heart. According to extensive data available to date, sildenafil citrate has been shown to pose minimal cardiovascular risks to healthy people taking this drug. Some precautions, however, are needed for patients with cardiovascular disease. Further clinical and basic investigation on the cardiovascular effects of sildenafil citrate is needed to assure proper treatment of ED in patients with cardiovascular disease.

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