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Sildenafil citrate, a selective phosphodiesterase type 5 inhibitor: urologic and cardiovascular implications

Abstract Erectile dysfunction (ED) occurs in varying degrees in an estimated 20 to 30 million American men and is associated with adverse effects on quality of life; particularly personal well-being, family and social interrelationships. Research into ED has focused primarily on the physiologic mechanisms of corpus cavernosum smooth muscle relaxation, and penile erection as the end result of smooth muscle relaxation. These processes are mediated by cholinergic, nonadrenergic, noncholinergic (NANC, e.g., nitric oxide), vasoactive intestinal peptide (VIP), and potentially calcitonin gene-related peptide (CGRP) containing nerves. Release of nitric oxide following sexual stimulation from non-adrenergic, noncholinergic nerves and vascular endothelium activates guanylyl cyclase and induces intracellular cGMP synthesis. In turn, cGMP results in lowering intracellular concentrations, inhibits contractility of the penile smooth muscle, and induces an erectile response. Phosphodiesterase type 5 (PDE 5) is the predominant enzyme responsible for cGMP hydrolysis in trabecular smooth muscle. Activation of PDE 5 terminates NO-induced, cGMP-mediated smooth muscle relaxation, and subsequent penile flaccidity. Sildenafil citrate is a potent PDE type 5 reversible and selective inhibitor which blocks cGMP hydrolysis effectively. FDA approval of sildenafil citrate as the first oral agent for ED in males has resulted in significant interest. We discuss the clinical and pharmacologic properties of sildenafil citrate as well as the urologic and cardiac implications.

Key words Male sexual dysfunction · Sildenafil citrate (Viagra) · Phosphodiesterase type 5 · Corpus cavernosum smooth muscle cells · cGMP · Cardiovascular

Erectile dysfunction (ED), the persistent inability to achieve or maintain an erection for satisfactory sexual performance [2, 17, 30] was self-reported in over half of the community-based respondents sampled between the ages of 40 and 70 years [13]. The prevalence increases with age, doubling for moderate and tripling for complete dysfunction ED between 40 and 70 years over the same time period. Along with age, treated diabetes mellitus, heart disease and hypertension, medications for diabetes, and cardiovascular disease and diminished values of high-density lipoproteins were found to predict complete ED.

Historically, treatment options for ED have evolved from penile implantation surgery (1970s), intracorporal injection of vasoactive agents (1980s), and transurethral insertion of prostaglandin E1 in 1997. The FDA approval of sildenafil citrate, the first oral on-demand agent for ED has heralded a significant advance in pharmacological strategies directed towards a diverse group of patients with ED.

This review will focus on the corporeal and cardiovascular effects of sildenafil citrate and the potential interactions with drugs used to treat cardiovascular diseases and conditions. The rationale for evaluating both penile and cardiovascular effects can be summarized as follows: (a) The risk factors associated with ED overlap extensively with risk factors associated with cardiovascular disease [25]. Thus, the prevalence of ED in patients with cardiovascular disease is higher than in the general population. In addition, sexual dysfunction is a common presenting factor to the urologist in men following a diagnosis of myocardial infarction and is most commonly attributed to potential sexual activity.
induced myocardial infarction; however, 10%–15% is due to organic causes of impotence [34]. (b) Sildenafil elevates the cyclic nucleotide second messenger for nitric oxide (NO), which is involved in regulating vascular smooth muscle tone, indicating a drug effect on the cardiovascular system. (c) Intense media coverage, in both the medical and lay press of cases of spontaneous death and serious cardiovascular events in men who had used sildenafil.

Pharmacology

Peripherally, erection is dependent on the state of trabecular smooth muscle tone. The balance between contractile systems (α-adrenergic, endothelin, thromboxane A2) and relaxatory systems (NO, VIP, CGRP, PGE1) determine this tone [2, 7, 9, 16, 29–31]. Pharmacologically mediated erection focuses on enhancing trabecular smooth muscle relaxation and providing penile rigidity. This can be accomplished in one of three ways: (a) receptor agonists which stimulate relaxatory pathways, (b) receptor antagonists which block contractile pathways, or (c) agents which elevate, enhance, or directly stimulate the synthesis of second messenger molecules such as cyclic AMP or cyclic GMP (cGMP) which promote trabecular smooth muscle relaxation. Elevation of the second messengers cAMP and/or cGMP in the trabecular smooth muscle favors the relaxatory pathways mediated by NO, VIP, and CGRP. Phosphodiesterase inhibitors, such as sildenafil citrate block the breakdown of cAMP and/or cGMP, potentiating the effects of these vasodilating substances.

Therapeutic advances: phosphodiesterase inhibitors

Sildenafil citrate acts indirectly by inhibiting phosphodiesterase type 5 hydrolysis of cGMP induced by NO [7, 28]. How does this affect erection? Upon stimulation (central nervous system or sensory), the nonadrenergic, noncholinergic (NANC) nerves release NO (produced by neural NO synthase) [2, 7, 28]. This NO activates guanylate cyclase in the vascular smooth muscle, increasing synthesis of cGMP which, in turn, leads to smooth muscle relaxation [16, 29, 31]. The end result is that the helicene resistance arterioles (which the cavernosal arteries feed) dilate, allowing an inflow of arterial blood; and the trabecular smooth muscle of the corpus cavernosum begins to relax [2, 7, 28]. There is a change in the blood PO₂ in the corpus cavernosum (25–40 to 90–100 mmHg erect) [24] and this increase in oxygen tension as well as some shear effects may activate the endothelial NO synthase, further contributing to NO production and increased cGMP [2, 7]. The major enzymatic activity in the corpus cavernosum that hydrolyzes cGMP and thus turns off the NO signal is phosphodiesterase type 5 (PDE5) [28]. Sildenafil citrate competitively inhibits PDE5 at concentrations of 5nM [28]. However, this medication alone does not induce erection. The high selectivity of sildenafil citrate and the special role of PDE5 in erection make this the current oral therapeutic of choice to treat ED [3, 22].

Pharmacologic selectivity

Sildenafil is a potent and selective inhibitor of PDE5, the predominant isoenzyme that metabolizes cGMP in the corpus cavernosum of the penis. cGMP is the second messenger of NO which is released in response to sexual stimulation from nerves and endothelial cells in the corpus cavernosum.

The tissue distribution of the phosphodiesterases and the degree of selectivity of sildenafil for the different types of phosphodiesterases determine the pharmacological properties of the drug [36]. Seven isoenzymes of phosphodiesterases have been identified in mammalian tissue [4]. PDE5 is localized in the human corpus cavernosum, in vascular, visceral, and trabecular smooth muscle, in skeletal muscle, and in platelets [4]. PDE5 has not been detected in human myocardium [36]. Sildenafil has a high affinity for PDE5 with favorable selectivity (>1000 fold) for human PDE5 over human PDE2 (predominately in adrenal cortex) and PDE4 (predominately in brain and lung lymphocytes) and (4000-fold greater selectivity for human PDE5 over human PDE3 (the isoenzyme that regulates cardiac contractility) [36]. PDE5 has no effect on cAMP in vascular tissue or in the myocardium.

Pharmacokinetics and metabolism of sildenafil

Following oral administration of sildenafil citrate, observed maximal plasma concentrations are reached within 60–120 min [33]. Approximately 96% of sildenafil and its metabolite are bound to plasma proteins. The reversible binding of sildenafil and its active metabolite determines the free active drug available to enter the smooth muscle and inhibit its target enzyme. Sildenafil is metabolized in the liver by cytochrome P450 and is converted into an active metabolite with characteristics similar to the parent compound. The half-life of sildenafil and its active metabolite is approximately 4 h [33].

Clinical experience with sildenafil

Several clinical trials with oral sildenafil have recently been reported [6, 17, 22, 33]. Sildenafil (25 mg, 50 mg, and 100 mg) or placebo was administered to 532 men with ED in a 24-week dose-response study, in a double-blind, placebo-controlled, multi-institutional trial. A proportional increase in scores for achieving and maintaining erections was noted with an increase in dose up to a maximum dose of 100 mg of sildenafil, the mean