

MINI REVIEW

PHARMACOLOGY OF SILDENAFIL CITRATE

DHANANJAY N. UMRANI AND RAMESH K. GOYAL*

*Department of Pharmacology,
L. M. College of Pharmacy,
Ahmedabad - 380 009*

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Abstract : Erectile dysfunction is a common and multi-factorial disease that strongly impairs the quality of life in men. During the past decade, many new therapeutic strategies have become available. But the need for oral treatment was strongly felt. This need appears to have been fulfilled with the introduction of sildenafil. The drug acts by enhancing smooth muscle relaxant effect of nitric oxide. A number of clinical studies have now proved its safety and efficacy. The drug has shaken social life all over the world and to accept this "magic pill" or not remains the question of individual choice.

Key words : erectile dysfunction sildenafil nitric oxide

Erectile dysfunction (ED) is a common and multi-factorial disease that strongly impairs the quality of life in men. It is expected to affect about 10-20 million men in the USA. In India, possibly because of the cultural, religious and male predominance nature of the society, data is not clearly available. During the past decade, many advances in the understanding of the pathophysiology of the erectile dysfunction have been made and new therapeutic strategies have become available. It has been established that an insufficient production of nitric oxide (NO) by penile nerve terminals and/or vascular endothelium may result in an impaired erection or impotence (1). ED is more common in older men, especially those with other chronic illnesses such as hypertension, atherosclerosis, and diabetes (2). The search

for a treatment that is easier to administer and fulfils at least the part of the 'ideal medical treatment' like effectiveness, nontoxic, easy to administer and affordable continues (3).

Intracavernous injection of papaverine was first used as monotherapy, but because of side effects such as priapism and fibrosis of the corpus cavernosum its use became limited. Later, combinations of papaverine with phentolamine and/or PGE-1 were used. Other combination therapies such as vasoactive intestinal peptide + phentolamine, or calcitonin gene related peptide+PGE-1, have been suggested (4).

Sildenafil (VIAGRA™), was introduced by Pfizer Inc. on 27th March 1998. Sildenafil citrate is chemically 5-[2-ethoxy-

*Corresponding Author

5-(4-methylpiperazine-1-ylsulfonyl phenyl) -1-methyl-3-propyl-6, 7-dihydro-1-H-pyrazolol [4-3-d] pyrimidin-7-one. With molecular formula- $C_{22}H_{30}N_6O_4$ (Fig. 1).

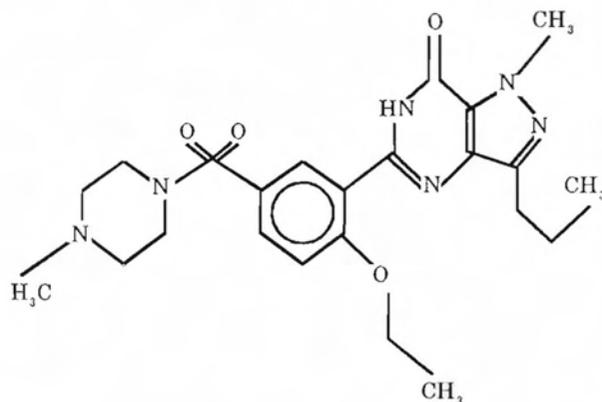


Fig. 1: Chemical structure of sildenafil citrate.

Mechanism of action :

Unlike previously approved treatments for impotence, sildenafil does not directly cause penile erection; but affects the response to sexual stimulation. The drug acts by enhancing the smooth muscle relaxant effects of nitric oxide (Fig. 2).

The physiologic mechanism of the erection of penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum; but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type V (PDE V), which is responsible for the degradation of cGMP in the corpus cavernosum. When

sexual stimulation causes local release levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effects in the absence of sexual stimulation (5).

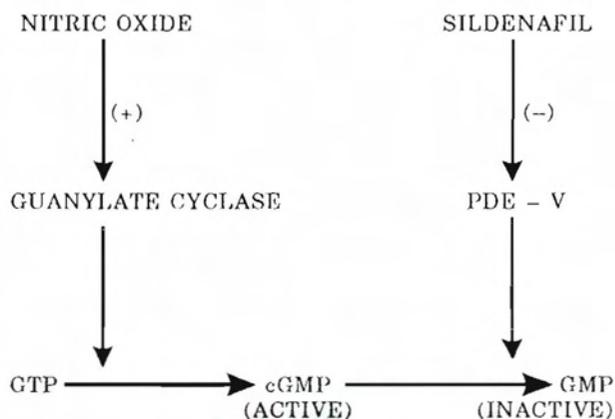


Fig. 2: Arrow diagram showing mechanism of action of sildenafil.

In vitro studies have shown that sildenafil is selective for PDE V. Its effect is more potent on PDE V than on other known phosphodiesterases (>80 fold for PDE I, >1000 fold for PDE II, PDE III and PDE IV). Approximately 4000 fold selectivity for PDE V versus PDE III is important as PDE is involved in control of cardiac contractility. Sildenafil is only about 10 fold as potent for PDE VI, an enzyme found in the retina. This lower selectivity is thought to be the basis for abnormalities related to colour vision observed with higher doses (6).

Pharmacodynamics :

In clinical studies, sildenafil has been assessed for its effect on the ability of men

was mixed in the remaining 18% of men. Efficacy was assessed by a self-administered questionnaire at week 8. In response to a global assessment question (Did treatment improve your erections?), 27.7% of the patients in the placebo group answered 'yes' compared to 47.7% of the sildenafil 4 mg group, 60.9% of the 25 mg group, 72.9% of the 50 mg group, and 77.8% of the 100 mg group, indicating that sildenafil appears to work in men with organic impotence as well as in those with psychogenic impotence (13).

A meta-analysis of 10 studies in 3361 patients with erectile dysfunction showed that sildenafil 50 or 100 mg was significantly more effective than placebo in terms of frequency of penetration and frequency of maintained erections (14). A meta-analysis of 8 studies of sildenafil in 2705 elderly patients showed that it was equally effective in elderly (≥ 65 years) as well as in younger patients with erectile dysfunction (15).

Pharmacokinetics and Metabolism:

Sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics is dose proportional over the recommended dose range (25, 50 and 100 gm). It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to parent molecule sildenafil. Both, sildenafil and its metabolite, have terminal half-lives of about 4 hours. Maximum observed plasma concentrations are reached within 30 to 120 min. of oral dosing in fasted state. When taken with a high fat meal, the rate of

absorption is reduced, with a mean delay in T_{max} of 60 min. and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (V_{ss}) for dildenafil is 105L. Sildenafil is cleaved predominantly by hepatic microsomal isoenzymes CYP 3A4 (major route) and CYP2C9 (minor route). The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. Sildenafil, and its major circulating N-desmethyl metabolite are both approx. 96% bound to the plasma proteins. After either oral or i.v. administration, sildenafil is excreted as metabolites predominantly in the faeces and to a lesser extent in the urine.

Drug Interactions:

As sildenafil metabolism is principally mediated by the cytochrome P450 isoforms 3A4 and 2C9 the inhibitors of these isoenzymes may reduce sildenafil clearance. e.g. cimetidine, erythromycin. It has been found to produce postural hypotension when combined with nitrates in hypertension probably because sildenafil potentiates action of NO; which is also the mediator for nitrates. So sildenafil should be strictly avoided in patients on nitrate therapy.

Adverse Reactions and precautions:

One out of 10 men in clinical trials developed blinding headaches. There can be sudden drops in blood pressure leading to blackouts. Although priapism never happened in trials, there is theoretical risk that men with sickle cell anemia or leukemia could develop priapism. Sometimes impotence is an early indication of heart disease, diabetes and some types of cancer.

Taking sildenafil could mask these life-threatening conditions (6).

Cardiovascular status of patient should be taken into consideration before initiating treatment for ED. The safety and efficacy of the combinations of sildenafil with other treatments for ED have not been studied. Therefore, use of such combinations is not recommended.

Phase II safety trials for sildenafil are underway in Europe, because it may also have the potential to help treat women with sexual dysfunction. To date, sildenafil has not been shown to have positive effects in women with this condition. Scientists are working to develop a second generation drug based on sildenafil that will work faster and be devoid of the adverse effects associated with sildenafil (6).

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