VIAGRA : IS IT A WONDER DRUG ?

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ABSTRACT

Male erectile dysfunction is common and frustrating after the age of forty years. Erectile dysfunction is a cause of misery, relationship difficulties, and significantly reduced quality of life. Sildenafil citrate (Viagra) has shown promising results in recently published clinical trials. Sildenafil is a potent and competitive inhibitor of cGMp specific phosphodiesterase-5, predominant isoenzyme in the human corpus cavernosum. It is effective in erectile dysfunction of diverse origin, however it requires a patent vascular system to be effective. It is not effective in patients with endocrinal impotence, loss of libido, premature ejaculation or infertility. Its main adverse effects are headache, flushing, dyspepsia, diarrhoea, nasal congestion, indigestion, visual disturbances, dizziness and rash. Ventricular tachycardia and acute myocardial infraction have been reported in patients of ischaemic heart disease after consumption of sildenafil. Six deaths have been reported in patients taking nitrates. In India it is likely to be prescribed by a primary care physician without complete evaluation of patient on complaint of impotence. Hence the ethical question of who should prescribe this drug should be addressed by medical fraternity and proper guidelines formulated to avoid misuse of sildenafil. Phosphodiesterase is distributed in nerve, central nervous system, and systemic vasculature, hence long-term effects of drug on these tissues has to be ascertained. It should be made mandatory to report all adverse drug reactions to ADR monitoring centres. It is a wonder for those who require it, but has potentially dangerous adverse effects and drug interactions and hence is and not a wonder pill for all kinds of impotence.

MJAFI 2001; 57 : 44-46

KEY WORDS : Erectile dysfunction; Impotence; Phosphodiesterase inhibitor; Sildenafil citrate.

Male erectile dysfunction has been defined as the persistent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance [1]. The prevalence of erectile dysfunction ranges from 52% in men aged 40-70 years to greater than 95% in men over 70 [2]. Improved understanding of peripheral and central mechanism for erection [3] has resulted in trials of various drugs [4-7]. Dr Simon Campbell while working on newer molecules for angina discovered sildenafil citrate, which has shown promising results in recently published clinical trials [8-10]. This drug was approved in USA by the FDA on 27 March 98 [11] and licence was granted for sale in Europe by European Medicine Evaluation Agency in third week of September 98 [12]. In India various companies are exploring the possibilities of its sale [13].

Chemical Structure

The chemical structure of the drug according to International Drug Nomenclature is 5-[2-Ethoxy-5-(4-methylpiperazin-1-sulphonyl)phenyl]-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-7-one(Fig-1).

Anatomy And Physiology of Erectile Function

The penis has two corpora cavernosa, which is surrounded by a thick fibrous sheath, the tunica albuginea. The erectile tissue consists of multiple, interconnected lacunae lined by vascular epithelium. Multiple helicine arteries branch off from cavernosal artery and open directly into these lacunar spaces. Blood is drained off through subtunical venules, which are compressed against thick tunica albuginea during erection and helps in maintaining tumescence [3]. Erection is a vascular event under neurogenic control. Tactile, auditory, visual or imaginative stimuli elicit penile erection by increasing central parasympathetic and decreasing sympathetic outflow. Decreased penile vascular resistance with resultant increased penile blood flow is considered a primary hemodynamic event in penile erection. Release of nitric oxide stimulates formation of cyclic guanosine monophosphate (cGMP) level in lacunar and arterial smooth

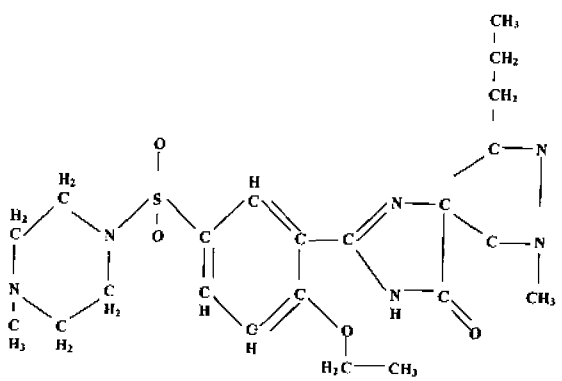

Fig. 1 : Chemical structure of sildenafil (Formula $C_{22}H_{30}N_6O_4S$)

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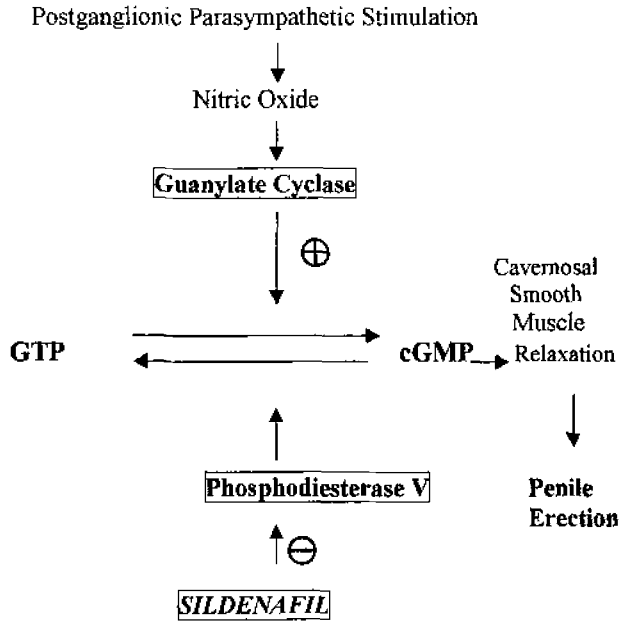

Fig. 2 : Mechanism of action of sildenafil

muscles, which causes relaxation of lacunar vascular cells. Papaverine is a direct vasodilator of penile vasculature [7]. This action is terminated by degradation of cGMP by phosphodiesterase type-5. Sympathetic activation leads to detumescence by endothelin mediated vasoconstriction. Prostaglandin E_1., receptor for which has been demonstrated on lacunae, relaxes smooth muscle through adenylate cyclase and cAMP formation [3].

Pharmacological Action

Sildenafil is a potent and competitive inhibitor of cGMP specific PDE5, predominant isoenzyme in the human corpus cavernosum and eye [8]. It decreases catabolism of cGMP, which enhances relaxation of the cavernosal smooth muscle, increases blood flow leading to increased intracavernosal pressure and penile rigidity (Fig-2). Sildenafil restores natural erectile response to various sexual stimuli but does not cause erection in the absence of stimuli. It is given in the dose of 50-100 mg orally. It is rapidly absorbed and maximum plasma levels are achieved in about one hour after oral administration. It has a mean half-life of three to five hours [9]. It is metabilised in the liver by cytochrome P450 (CYP) isoforms 3A4 and 2C9.

Therapeutic Effect

It is effective in erectile dysfunction of diverse origin, however it requires patent vascular system to be effective. Hence this is not effective in severe arterial or venous insufficiency. Boolell et al [8,9] first reported its effectiveness in a double blind placebo controlled, four way cross over trial in erectile dysfunction of psychogenic origin in twelve patients. Goldstein et al [10] have demonstrated its effectiveness in men with erectile dysfunction of diverse causes e.g. organic, psychological and mixed Sildenafil improved erectile function, orgasmic function and intercourse satisfaction. However only 70% of all sexual attempts successfully ended in sexual intercourse compared to 22% in placebo group. There was an increase in efficacy from 56% to 84% with the graded dose of 25 mg, 50mg and 100 mg. However mean scores for achievement and maintenance of erection were not the same as with normal men. It had no effect on sexual desire as expected from its mechanism of action. In a recent meta analysis of 10 double blind, placebo controlled trials involving 3361 patients with erectile dysfunction (organic 60%, psychogenic 15%, and mixed 25%) response rate for penetration was 46% compared to 8% in palcebo group, however partial improvement in erectile function was observed in 71% patients [14]. Significant improvement was also demonstrated in psychological assessment of patients receiving sildenafil in the form of positive well being, self control, decreased depressive component and satisfactory relationship with partner [15]. It is not effective in patients with endocrinal impotence, loss of libido, premature ejaculation or infertility.

Adverse Events

This drug is well tolerated. Its main adverse events are headache (16%), flushing 10%), dyspepsia (7%), diarrhoea (4.9%), nasal congestion (4%), indigestion (%), visual disturbances (3%), dizziness and rash (2%) [9,10]. Patients reported seeing blue haze and transient increased brightness when taking doses over 200 mg. This may cause difficulty in distinguishing colour, hence pilots should be restrained from consuming this drug six hours before flying [16]. Ventricular tachycardia occurred in two patients with history of extensive myocardial infarction within one hour of ingestion of sildenafil and sexual activity. Acute myocardial infarction has been reported in a 65 year old man without coronary risk factor after half an hour of consumption of sildenafil before performing sexual activity [17]. 69 deaths have been reported from USA among men taking sildenafil during March to July 1998, however no cause and effect facility has yet been proved [18]. Priapism has not been reported with sildenafil as reported with various other pharmacological therapy [4-7] of erectile dysfunction.

Drug Interaction

Sildenafil enhances the muscle relaxant effect of nitric oxide, hence it potentiates blood pressure lower-

ing effect of organic nitrates. 6 deaths have been reported by US FDA in patients taking nitrates, however no causal link has been established [11]. The manufacturing company has issued a warning that patients with ischemic heart disease taking nitrates should be prescribed sildenafil with caution. Drugs, which inhibit cytochrome P450 system, will increase the serum concentration of sildenafil, and cytochrome inducers will decrease it. No significant interaction has been reported with oral hypoglycemic agents, antihypertensives, warfarin, aspirin and alcohol.

Ethical Issue

It is likely to be prescribed by a primary care physician without complete evaluation of patient on complaint of impotence. Hence the ethical question of who should prescribe this drug should be addressed by medical fraternity by consensus and proper guidelines formulated to avoid misuse of sildenafil. In India drugs are commonly sold on prescription of varied forms of medical practitioners and even without prescription. Already there is news of availability of this drug under the counter and of spurious quality [19]. In Armed Forces this drug may be demanded with intention to enhance sexual performance. However all who seek this drug should be advised to undergo proper evaluation at endocrine and urology centres before this drug is advised.

Erectile dysfunction is a cause of misery, relationship difficulties, and significantly reduced quality of life for men and their partners. All primary care physicians should be competent in performing basic evaluation of risk factors and discussing various therapeutic avenues available. Phosphodieterase is distributed in nerves, central nervous system, and systemic vasculature, hence long-term effects, of drugs on these tissue have to be ascertained. It should be made mandatory to report all adverse drug reactions (ADR) to ADR monitoring centres [20]. With the advent of drugs acting on specific site on penile tissue, further avenues have opened up for possibility of introduction of other drugs of same group or development of drugs that may act by different mechanism. It is a wonder for those who require but has potentially dangerous adverse effect and drug interaction, and is not a wonder pill for all kinds of impotence.

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