Drug Update

SILDENAFIL-ORAL MEDICATION FOR ERECTILE DYSFUNCTION-A REVIEW

Lt Col N SRINATH *, Col SV KOTWAL +

ABSTRACT

Problem of male erectile dysfunction has been better defined, recognised and being treated in the recent times. However, the intracavernosal injection of vaso-active materials and penile prosthesis implantation were only the viable options available. Sildenafil, which is a specific phosphodiesterase type V inhibitor, enhances erection on sexual arousal by increasing the quantity of cyclic guanosine monophosphate in the corpora cavernosa. This has revolutionized the treatment of erectile dysfunction. Though the drug appears very promising with little side effects, many questions regarding efficacy, safety, misuse and overuse need to be addressed.

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Introduction

Erectile dysfunction, the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, is estimated to affect up to 30 million men in the United States [1]. The prevalence of the problem increases with age. The available treatments include vacuum erection devices, intracavernosal injection of vaso-active agents [2], transurethral delivery of alprostadil (prostaglandin E1) [3], implantation of penile prosthesis and venous or arterial surgery. No effective oral therapy for erectile dysfunction was available [4].

Sildenafil a compound developed by Pfizer ® was being investigated as an anti-anginal and anti-hypertensive agent. It was disappointing as an anti-hypertensive agent but many patients in the study reported that they had the best sexual experience in recent times. This lead to further investigations as a therapy for erectile dysfunction.

Mechanism of Action

Normal penile erection depends on the relaxation of smooth muscle in the corpora cavernosa. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide (NO), which stimulates the formation of cyclic guanosine monophosphate (cyclic GMP) by guanylate cyclase [5,6]. The mechanism by which cyclic GMP stimulates relaxation of smooth muscles remains to be elucidated. Sildenafil has no direct relaxant effect on isolated human corpus caver-

nosum. Sildenafil is a selective inhibitor of cyclic GMP specific phosphodiesterase (PDE) type 5, the predominant enzyme metabolizing cyclic GMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE 5 by sildenafil causes increased levels of cyclic-GMP in corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect on sexual stimulation. Sildenafil is extremely selective on PDE 5, compared to PDE1,2,3 and 4 but only 10 fold as potent for PDE5 compared to PDE6, an enzyme found in retina and believed to be involved in phototransduction. This lower sensitivity is thought to be the basis of abnormalities related to colour vision observed with higher doses [7]. Sildenafil is effective only when there is partial erection. Whereas if there is severe arteriogenic or venogenic impotence, corporal smooth muscle fibrosis or anatomical penile deformities/defects, sildenafil is ineffective.

Pharmacodynamics and Metabolism

Sildenafil is rapidly absorbed after oral administration with absolute bioavailability of about 40%. Maximal plasma concentrations are achieved within one hour after oral administration with mean terminal half-life of three to five hours [8]. Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route), hepatic microsomal enzymes. The drug is excreted in faeces (80%) and urine (13%) as metabolites.

* Classified Specialist Surgery and Urologist, + Senior Adviser Surgery and Urology, Department of Urology, Army Hospital (Referral & Research), Delhi Cantt, Delhi- 110010.

Pharmacodynamics

In eight double blind placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by penile plethysmography after Sildenafil administration compared with placebo [9]. The effect was maximal at about one hour after administration and lasted for about four hours. Single oral doses of sildenafil upto 100 mg produced no clinically relevant changes in ECGs of normal volunteers and produced an average blood pressure decrease of 10-mm of Hg in normal volunteers. Larger but transient effects on blood pressure were recorded in patients receiving nitrates concomitantly. Mild, transient, dose-related impairment of colour discrimination (blue/green) was recorded with peak effects near the time of peak plasma levels.

Dosage and Administration

The Sildenafil is recommended in the dosage of 50 mg administered orally one hour prior to sexual activity. Maximum dosage permitted is 100 mg. The drug is recommended to be taken about an hour before anticipated sexual activity and only once a day. All patients before being put on Sildenafil should undergo a general cardiac check up. Patients with retinal conditions should be cautious about using Sildenafil because the drug has been associated with visual disturbances. Sildenafil is contraindicated in patients taking nitrates because of the risk of a sudden large drop in blood pressure.

Adverse Reactions

Visual Disturbances: The American Academy of Ophthalmology has warned patients using Sildenafil that the drug may have adverse effects on vision. Patients have reported transient visual disturbances described as light sensitivity and seeing a bluish colour tinge. 3% of patients reported visual disturbances compared to no placebo recipients, in a series of flexible titration studies carried out for 4-26 weeks [10].

Common adverse events: The most common adverse events described have been Headache (11%), facial flushing (4-8%), dyspepsia (4-5%) and diarrhoea (4%). No case of priapism was reported. All the adverse reactions were dose related and no case of tachyphylaxis has been reported [11].

Hypotensive effects: Sildenafil should not be taken by men who are on nitrates because it potentiates the hypotensive effects of nitrates (by its action on nitric oxide/cyclic GMP pathway). The expert panel of American College of Cardiology warned that the pa-

tients taking Sildenafil should not be administered nitrates in an emergency because of the risk of sudden large drop in blood pressure [12].

Therapeutic Trials

Initial placebo controlled pilot studies were done in US and UK which showed significantly improved erectile response during visual sexual stimulation. This was followed by phase I, II and III clinical trials in US and elsewhere.

The different studies done were fixed dose vs. dose escalation, single blind, placebo run-in to double blind phase and long-term open-label extension studies. The studies were done in men above age of 18 who were diagnosed to be suffering from erectile dysfunction both organic and psychogenic. Efficacy was assessed by using responses to question three (frequency of penetration) and question four (maintenance of erection after penetration) of 15 question International Index of Erectile Function questionnaire [13]. The responses to the above questions were rated on a scale of 1 (almost never or never) to 5 (almost always or always). Many of the studies included interviews with the sexual partners. All studies showed that Sildenafil consistently improved erectile function and increased the success of intercourse 3 to 4 times only on sexual arousal. Most men took the drug an hour before the anticipated sexual activity. The drug did not increase the non-sexual 'waking' erections and did not increase the frequency and intensity of sexual desire.

A multicentre double blind randomized study in 861 patients with erectile dysfunction of various origins showed that Sildenafil significantly improved the erectile function and quadrupled the success of intercourse, with efficacy maintained for at least 6 months [14]. A meta-analysis of 10 studies in 3,361 patients with erectile dysfunction showed that Sildenafil 50 mg or 100 mg was significantly more effective than placebo in terms of frequency of penetration and frequency of maintained erection [15]. A meta-analysis of 8 studies of Sildenafil in 2705 elderly patients showed that it was equally as effective in elderly (65 years) as in younger patients with erectile dysfunction [16].

In a study of patients with diabetes mellitus and erectile dysfunction who took Sildenafil, 57% of recipients of Sildenafil stated that the treatment improved their erections compared with 10% of placebo recipients [17]. In a small, randomized study involving spinal cord injury patients with erectile dysfunction, Sildenafil improved erections and recipients reported significantly greater satisfaction with their sex life

[18]. Overall, the drug was effective in 90% of patients with psychogenic erectile dysfunction and 60-70% of patients with organic erectile dysfunction.

Launch Information

Pfizer pharmaceutical company applied for launching Sildenafil in fall of 1997. After perusing all the studies, the drug was launched in US as Viagra in 25, 50 and 100 mg tablets, after approval by FDA on 27 March 1998 for patients with erectile dysfunction. This was followed by advertising blitzkrieg by the company and it caught the imagination of the people. 40,000 prescriptions were being filled up at two weeks after launch and it has already become the biggest successful launch of any drug for all times, with sales crossing more than 4 billion US dollars. It has been launched in San Marino and Brazil. It is registered for launch pending approval in Mexico, Canada etc., and in pre-registration or Phase II III trials in European Union.

Concerns on use of sildenafil

Most of the therapeutic trials done and published by doctors who have been paid or honorary consultants to the drug manufacturing companies. More data that is objective is likely to emerge once the drug is tested on a much larger scale by more doctors. Lot of concern has been generated by reported death of patients after taking sildenafil and engaged in sexual activity. On 09 June 1998 FDA issued a statement regarding 16 reported deaths after Sildenafil was taken. All patients were in 60-70 yr age group with concomitant ischemic heart disease or hypertension. Nine patients were reported to have collapsed or developed chest pain during sexual activity following administration of Sildenafil. In 3 patients, the death was reported to be due to stroke and in 6 others it was due to cardiac arrhythmia or heart failure. In others, the cause was not listed. On 11 Aug 98 FDA issued another warning not to prescribe sildenafil to patients who are on nitrates or on amyl nitrate as it can result in precipitous fall in blood pressure. There is considerable concern regarding the physical condition of many of the elderly patients with heart disease and impotence to tolerate the rigors of sexual activity after taking Sildenafil. In fact, vasculogenic impotence is one of the markers of atherosclerotic involvement of coronaries.

There is considerable concern regarding recreational uses of Sildenafil by people who do not have erectile dysfunction the moral issues arising out of it. Some of the governments including India have not yet given the approval citing the above grounds. Already the pill is being used in party circuit and any combina-

tion with amyl nitrate, which is sometimes used as an agent inducing 'high' may result in precipitous drop in blood pressure.

New areas of research

The Pfizer is already working on a wafer preparation of Sildenafil to give almost an immediate effect. Other drugs being developed as an oral pill for impotence are apomorphine and phentolamine. However, both have not shown much promise in initial trials. Aprodastil (prostaglandin E1) is being tried as an intraurethral pessary and as topical gel. There are a number of trials going on for use of Sildenafil in women to enhance the sexual experience. It is well known that women also have erectile tissues and many scientists have come to believe that the causes of male and female impotence may not be that far apart after all. Currently Phase II trials are on in Europe for use of Sildenafil for women.

Conclusion

Millions of men have been waiting a long time, mostly in silence, for a simple treatment that would solve their inability to achieve or maintain an erection. Development of intracavernous injection of vasoactive materials for erection introduced in 1983 was the first major advance in treatment of erectile dysfunction. The American Urological Association Panel on the Treatment of Organic Erectile Dysfunction stated that the ultimate goal is a therapy that is reliable, has minimal side effects, and that is simple to use. Sildenafil appears to meet these specifications. Oral therapy permits discreet administration and is non invasive than some other treatment options such as injections into the corpus cavernosum, transurethral drug delivery, and penile prosthesis implantation. With widespread use of Sildenafil, more data on its efficacy and safety is likely to emerge over the years. Women too are likely to benefit from these drugs in achieving a more satisfying sexual experience.

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