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Tadalafil as new oral treatment for erectile dysfunction: a review

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ABSTRACT

Erectile dysfunction (ED) is a disability to achieve or sustain an erection to do satisfying intercourse, that occur at least for three months. Erectile dysfunction patients are significantly increasing every year, especially in male age 40-70 years old. Tadalafil inhibit phosphodiesterase type 5 (PDE5) enzyme 10,000 times more potent than PDE1, PDE2, PDE4 and PDE7; 700 times more potent than PDE6; 900 times more potent than PDE8, PDE9, PDE10, and also 14 times more potent than PDE11A₁. In elderly, erectile dysfunction commonly is caused by aging process. In other hand, the condition in young adult is usually caused by physiologic factor or stress. Some studies reported that there is no significant difference between the tadalafil's pharmacokinetic in young adult

and elderly, also in patient with or without diabetes mellitus (DM). The dose of tadalafil does not need to be regulated in patients who have liver function disturbance, DM, elderly, renal function disturbance, patients who take medicine like erythromycin, ketoconazole, itraconazole, protease inhibitor, and medicine that inhibit the CYP3A4 system. Several clinical studies reported that tadalafil can increase erection significantly and the patient able to do sex intercourse successfully. Tadalafil does not affect the blood pressure; heart rate; concentration, motility, and morphology of the sperm; and also does not cause eye disturbance. There was no evidence of teratogenicity, embryotoxicity and foetotoxicity in rats that were given tadalafil 1000 mg/kg/day.

Keywords: tadalafil, erectile dysfunction, pharmacokinetic

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INTRODUCTION

Erectile dysfunction is the inability to achieve or to sustain an erection for satisfactory sexual intercourse for at least 3 months. Patients with erectile dysfunction each year increased significantly in number, which the highest prevalence occurs in men aged 40-70 years old.^{1,2} In the United States an estimated number of patients with erectile dysfunction has reached more than 30 million people, while the total was more than 150 million worldwide and only 10% of them are getting sufficient therapy. With increasing world population and old age population, it is estimated that in 2025 patients with ED in the USA will reach 322 million people.¹

Erectile dysfunction increases with age, usually affecting males over the age of forty, but it can also affect men aged twenty or thirty years. In older people, this disease is usually caused by the aging process, whereas patients with erectile dysfunction in younger age is usually caused by psychological or stress factors and usually temporary. The stress factors can cause the body's immune system decline, and disturb several other systems in the body.² ED occurs in men with cardiovascular disease, DM, hypertension, hypercholesterolemia, trauma of the spinal cord, prostate cancer, post orogenital surgery. It also sometimes occurs in patients who

receive antihypertensive drugs, antidepressants, anti-arrhythmic drugs and alcohol drinkers.³

Since the introduction of sildenafil with the trade name of Viagra in 1998, it is used very commonly by patients with ED worldwide. The discovery is a revolutionary invention in the field of medicine. Tadalafil under the brand name Cialis was introduced by Eli Lilly in Indianapolis in 2003, which the drug is a second-generation drug selectively inhibiting the PDE5 enzyme. Since then, the ED sufferers start to use tadalafil. Several studies have reported that the drug is more potent and have less serious side effects than sildenafil.⁴

Erection and Etiology of Erectile Dysfunction

Erection is a neurovascular process that starts from sexual stimulation gained in the form of vision, hearing, and feeling that signals the brain. The stimulus resulted production of nitric oxide (NO) by non-andrenergic non-cholinergic (NANC) nerve in the penis. After that, NO diffuses into smooth muscle cells that signals the production of guanylate cyclase, which serves to transform guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The increase of cGMP causes relaxation of the smooth muscle in corpus cavernosum, thus increasing the blood flow into

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sinusoids. The entry of the maximum blood flow to the corpus cavernosum causing the ends of the corpus cavernosum vein narrowed then closed, causing blood stuck in corpus cavernosum then resulting penile erection.⁵

The next process is the breakdown of cGMP by the PDE5 enzyme into GMP and GTP. cGMP breakdown causes contraction of smooth muscles so that blood flow to the penis stops. Cessation of blood flow to the penis causes the penis to be flaccid. An erection will not occur normally when levels of cGMP in the corpus cavernosum smooth muscle is not sufficient to cause corpus cavernosum smooth muscle relaxation. If there is no sexual stimulation, then the activity of nerve-nitric oxide pathway will not be effective.⁵

Several experts argue that the pathophysiology of ED are: (1) a metabolic imbalance between contractile factors (norepinephrine, endothelins, and prostanoid) and the relaxation factors (vasoactive intestinal polypeptide and NO) in the corpus cavernosum; (2) The imbalance between trabecular muscle and connective tissue.¹ Mainly, the ED are due to two factors: organic factors and psychogenic factors. In the United States, approximately 10% ED is caused by organic factors and 90% due to psychogenic factors.⁶ ED may be a sign caused by several pathological disorders such as cardiovascular disease, DM, organic diseases that were not diagnosed such as hypertension, hyperlipidemia, other kind of heart diseases, neurologic diseases, and endocrine disorders.⁷

Erectile Dysfunction Treatment with Tadalafil

Sildenafil with famous trade name Viagra has been used commonly for a long time by the patients with erectile dysfunction. While the drug has recently been developed is tadalafil, known by the trade name Cialis. The usefulness of tadalafil for the treatment of erectile dysfunction has been approved by the Food and Drug Administration (FDA) of United States. Superiority of tadalafil compared with sildenafil are better effect, longer half time, and does not cause a disturbed vision.⁸

Tadalafil Structure

Tadalafil is an oral erectile dysfunction drug which selectively inhibits PDE5 enzyme, with a chemical structure as shown in [figure 1](#).

Pharmacokinetics

Tadalafil oral medications are available with various doses: 2.5 mg; 5 mg; 10 mg; and 20 mg.² In adults, tadalafil 20 mg administered approximately 30 minutes before sexual activity begins. Tadalafil consumption per oral will be absorbed rapidly

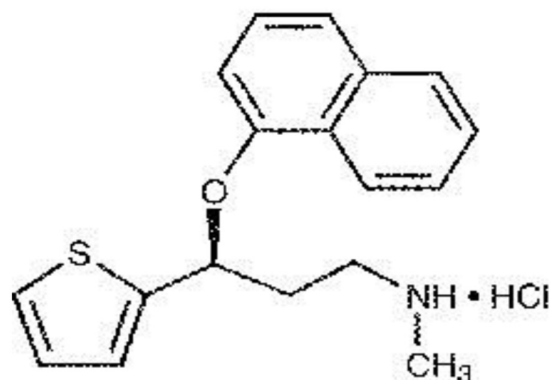


Figure 1 Pyrazino (1,2; 1,6) pyrido (3,4-b) indole-1,4-dion, 6-(1,3 benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl (6 R,12aR)

with maximum plasma concentration 2 hours after administration. This drug absorption is not affected by food so that it can be given with or without food.⁹ The distribution to the tissue with an average steady-state volume of distribution is 63 L. After oral administration, 94% bound to plasma proteins and this bond is not affected by impaired renal function. These drugs primarily metabolized in the liver by the cytochrome P450 (CYP) 3A4 isoform, forming methylcatechol and methylcatechol glucuronide. After metabolized, tadalafil will be excreted mainly through feces (61%) and urine (36%). Tadalafil can dissolve in water or fat. Tadalafil solubility in water is better than the sildenafil.² Study of tadalafil in vitro by the company Lilly ICOS LLC found that tadalafil has no effect on CYP3A4 activity.

Several studies have reported that tadalafil pharmacokinetics have no significant differences between young and older patients, as well as in patients with or without DM. The results also showed that food does not affect the absorption of tadalafil in the body. Similarly, the consumption of alcohol before taking tadalafil has no significant impact on the absorption of the drug in the body. The effect has no significant clinical differences and does not require adaptation dosages.¹⁰ One clinical study among patients with impaired renal function with creatinine clearance 31-80 mL/min and in patients with renal failure undergoing hemodialysis were given tadalafil 10 mg obtained comparable tadalafil exposure (AUC) with the healthy subjects. Tadalafil treatment in patients with hepatic dysfunction, patients with diabetes, the elderly, those with impaired renal function, patients who consume several drugs including erythromycin, ketoconazole, itraconazole protease inhibitors and other drugs that inhibit the CYP3A4 system does not require dosage adaptation.¹¹ A clinical study in patients with erectile dysfunction were given tadalafil 20 mg reported erectogenic response occurs

after 16 minutes of administration with active period of around 36 hours.⁹

Pharmacodynamic

Most of the research leading to the production and development of PDE5 enzyme inhibition. The molecular structure of tadalafil is different compared to sildenafil and vardenafil, but all of them work in the same mechanism. Clinical studies showed that administration of 10 mg and 20 mg of tadalafil 30-60 minutes before sexual activity have 30 to 36 hours effective state. In vitro studies showed that tadalafil selectively inhibit PDE5 enzyme. The study showed that tadalafil inhibition of the PDE5 enzyme was 10,000 times more potent than PDE1, PDE2, PDE4 and PDE7; 700 times more potent than the PDE6; 9,000 times more potent than PDE8, PDE9 and PDE10 and 14 times more potent than PDE11A1.¹² PDE5 enzyme is widely found in the corpus cavernosum smooth muscle, vascular, visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. Clinical studies on 571 patients who received tadalafil obtained significant improvement in erectile function and able to have successful intercourse. Some researches reported that administration of Tadalafil has no effect on blood pressure, heart rate, and cause no visual disruption.³ Other study of 103 men were given 10 mg tadalafil for 6 months had no effect on the concentration, movement, and morphology of the sperm. Research on 3,250 patients in 16 clinics with different levels of ED (mild, moderate and severe), age ranged from 21-86 years old is given tadalafil with a range of 2-100 mg dose reported a significant erection as much as 86%, 83%, and 72% for mild, moderate, and severe case, respectively. Clinical research on 103 men given 10-20 mg tadalafil for 6 months found the levels of testosterone, LH, and FSH are not significantly different compared to patients using placebo.¹³

In one study of 348 men with ED, the participants were given 20 mg of tadalafil for 8 weeks then instructed to engage in sexual activity 24 hours or 36 hours after dosing. The research found that ED patients who were given tadalafil can have significant sexual intercourse ($p < 0.001$) compared to controls. In a study of 4000 patients, it was reported that the incidence of myocardial infarction was similar with no significant difference between treatment (using 20 mg of tadalafil) and control groups (using placebo). The side effects that are reported were more than 5% of people had headaches, flushing and dyspepsia, while other studies had less than 2%.³ A study in Europe found that among sufferers with mild to moderate ED who were given tadalafil 50 mg, 93% of them reported having sex successfully. Other studies with doses of 2-25 mg obtained

88% of patients may have erections and more than 73% can have sex with success. Other study of DM patients with ED found that the patients who were given a dose of 10 mg and 20 mg tadalafil obtained 56% and 64% to get an erection compared to only 25% using placebo.¹

Mechanism of Action

All three PDE-5 inhibitors such as sildenafil, vardenafil and tadalafil have same mechanism of action that all of them competitively inhibits the interaction of cGMP and cyclic nucleotide PDE-5 enzyme. Sildenafil and vardenafil inhibit PDE5 and PDE6 enzyme, while tadalafil inhibits PDE5 and PDE11. PDE-6 is present in the retina and is hydrolyzed by cGMP, whereas PDE-11 found in muscle, prostate, kidney, liver, hypothalamus, saliva gland and testes and will be hydrolyzed by cAMP and cGMP. Sildenafil and vardenafil may cause visual impairments so careful attention must be made for pilot or other similar occupation, while tadalafil does not.⁴

Side Effects

In clinical studies involving 4000 subjects aged between 19-86 years old, including more than 230 patients who received treatment for one year and more than 720 patients who received treatment for 6 months, reported that side effects are not significantly different compared to placebo. In general, the most frequent side effects are headache and abdominal pain, while less complaints such as rhinitis, myalgia, and vasodilatation.² When tadalafil was given along with the alpha adrenergic blockers drugs eg, Doxazosin, Prazosin, and Terazosin, they can cause a significant decrease in blood pressure, but this effect did not happen when administered with tamsulosin. In patients who are in nitrate treatment, nitrate is allowed at least 48 hours after taking tadalafil and hemodynamic of the patients should be monitored. There were no evidence of teratogenicity, embryotoxicity and fetotoxicity in rats and mice that received tadalafil 1000 mg/ kg/ day.⁹

Contraindications

Tadalafil is contraindicated in patients who consume nitrates, alpha blockers, had history of heart attack or stroke in the past 6 months. It is also contraindicated in patients with uncontrolled hypertension, hypotension, unstable angina, liver disease and severe kidney disease, leukemia, multiple myelomas and sickle cell anemia.¹²

SUMMARY

Patients with erectile dysfunction each year increased significantly, with the highest prevalence

occurs in men aged 40-70 years. In older population, ED is usually caused by the aging process, while in young patient, it is usually caused due to psychological factors or stress and usually temporary. After the introduction of tadalafil under the brand name Cialis by Eli Lilly from Indianapolis in 2003, it is widely used for ED patients. Tadalafil is a second generation drug selectively inhibiting the PDE5 enzyme 10,000 times more potent than PDE1, PDE2, PDE4 and PDE7; 700 times more potent than the PDE6; 9,000 times more potent than PDE8, PDE9 and PDE10 and 14 times more potent than PDE11A₁. The absorption of this drug is not affected by food ingestion so that it can be given with or after a meal. Clinical studies of tadalafil reported that patients with erectile dysfunction had significant erection and able to have intercourse with success. Other studies also reported that administration of tadalafil has no effect on blood pressure, heart rate, vision, sperm, and cardiovascular system. In general, reported side effects are: dizziness, stomach pain, rhinitis, and myalgia.

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