e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

Review article

A REVIEW ON PDE-5 INHIBITORS AND TREATMENT APPROACHES OF ERECTILE DYSFUNCTION

Pranathi Reddy R[1]*, Bhavani D[1], Aleem Sarwar[2] , Deepika S[1]

[1]Pharm. D. student, [2]Assistant Professor, Sri Venkateshwara College of Pharmacy, RVS Nagar, Chittoor 517127, Andhra Pradesh, India.

ABSTRACT

Erectile dysfunction (ED) is defined as the inability of a man to achieve or maintain erection for required time for intercourse. Sexual activity is one of the main function for maintaining god quality of life. Treatment approaches of ED includes both pharmacological therapy and non-pharmacological therapy. Pharmacologically specific class of drugs like PDE 5 inhibitors and non-pharmacological approach, which includes use of aphrodisiac potentials and other therapies like sex therapy, vacuum erection device therapy, surgical procedures are available. PDE5 inhibitors include the drugs like avanafil, sildenafil citrate, tadalafil and vardenafil. The present review, describes the detail information about the pharmacokinetics and pharmacodynamics of PDE5 inhibitors. A detailed comparison and differentiation between each drug of the class (PDE5 inhibitors) with their adverse effects, contraindication, precautions, and alternative treatment approaches for ED. And also the non-pharmacological approaches with their adverse effects and contraindication.

Key Words:- Erectile dysfunction, PDE 5 inhibitors, Non-pharmacological therapy.

Access this article online

Home page: http://ijptjournal.com/

DOI: http://dx.doi.org/10.21276/ijpt.2017.8.4.5

Quick Response code

Received:25.07.17 **Revised**:12.07.17 **Accepted**:15.08.17

Corresponding Author

Pranathi Reddy R
Pharm. D, Department of Pharmacy Practice, Sri Venkateshwara College of Pharmacy, RVS Nagar, Chittoor 517127, Andhra Pradesh, India.
Email:- pranathi346@gmail.com

INTRODUCTION

Erectile dysfunction (ED) is a sexual dysfunction, when it is hard to get or keep an erection firm to have an intercourse (anonymous 1) which results from health or emotional problems or from both. As many as 152 million men all over the world where reportedly affected with ED. It is common and men experience it one or the other time, but considered as erectile dysfunction if one experience it more than half of the times. Recently the global projection survey results suggest that as many as 322 million men will experience ED by 2025 (Benchekroun A *et al*., 2003). Moreover, increased risk for ED has been associated with presence of benign prostatic hyperplastic hyperplasia and with treatment for prostatic cancer (Namasivayam S *et al*., 2001). In more than 50% of patients aging above 40years are developing ED. However other trending factors include aging where the use of medications of chronic diseases like diabetes, hypercholesterolemia, renal disease, and depression will exacerbate ED. The most common culprits for medically induced ED are antihypertensive drugs and antidepressants, as both ED and cardiovascular disease share similar atherogenic risk factors and a common etiology leading to endothelial cell injury and dysfunction (Ralph G. Brindis *et al*., 2003).

Sildenafil citrate, avanafil, tadalafil,vardenafil have been proven as the best drugs of choice for ED showing its effect in many untreated ED patients with their resumed quality of life{QOL}. Sildenafil is the first phosphodiesterase type 5(PDE5) oral drug approved for the treatment of erectile dysfunction. The other drugs in use for treating ED include vardenafil and tadalafil (Giuliano F *et al*., 2009). However, sildenafil acts by selective inhibition

of phosphodiesterase in addition to its presence in corpus cavernosum phosphodiesterase in found in other tissues in lower concentrations, including vascular, visceral smooth muscles, platelets, cardiac muscles but not in cardiac myocytes. Because of this selective PDE5 activity in cardiovascular tissues, sildenafil is not associated with deleterious cardiovascular effects unless combined with contraindicated drugs like drugs containing organic nitrates (Levinson IP, 2003).

PHARMACOLOGICAL APPROACH FOR ERECTILE DYSFUNCTION (ED):

Pharmacokinetics of PDE5 inhibitors:

All the tree drugs namely Sildenafil, vardenafil; avanafil and tadalafil have rapid onset of action and are phosphodiesterase inhibitors. However, they differ in their percentages of bioavailability, such as 40% of bioavailability for sildenafil and 15% for vardenafil. Whereas the bioavailability of tadalafil is not known (Blount MA., 2004). Half-life of sildenafil is 3.8hrs, and 17.5hrs for tadalafil and 3.9hrs for vardenafil (Porst H., 2002). Subsequently as the half life increases the duration of action of the drug also increases, tadalafil has the longest duration of action among these three drugs (Doggrell S, 2007).

All the three phosphodiesterase inhibitors (PDE5) are metabolized by cytochrome P450 3A4 enzyme. Vardenafil undergoes substantial first pass metabolism. Hence, a lower starting dose of vardenafil is recommended in moderate hepatic failure patients. Selective inhibitors like cimetidine and non-selective inhibitors like erythromycin, ketoconazole, ritonavir are known to increase the plasma levels of the drugs, hence contraindicated for concomitant use (Gupta M *et al*., 2005). All the three drugs are well absorbed orally and a heavy fat meal may decrease the or affect the onset of action of vardenafil (Rajagopalan P *et al*., 2003), but not tadalafil (Forgue ST *et al*., 2006). Because this a sub-lingual preparation of sildenafil has been developed to prevent from drug-food interactions (Deveci *et al*., 2004).

Thus, vardenafil, sildenafil, avanafil are short acting selective phosphodiesterase type 5 inhibitors where tadalafil is the long acting PDE5 inhibitors with half-life ranging about 17.5 hours(Eli Lilly. 2011), and which need not be taken before 1hr of sexual intercourse unlike other PDE5 inhibitors.

MECHANISM OF ACTION OF PDE5 INHIBITORS:

Cyclic Guanosine monophosphate(cGMP) is the intercellular trigger for penile erection with is brought by release of nitric oxide(NO) GMP is the intracellular trigger for penile erection. In erectile dysfunction, the release of NO is decreased which brings about the conformational abnormalities in relaxation of smooth muscles (Boolell M *et al*., 1996). Thus, PDE5 inhibitors initiates the release of NO from L- arginine under the control of nitric oxide synthase (NOS). This NO binds to guanylyl cyclase causing a conformational change which results in release of cGMP dependent protein kinases and other several proteins. Protein kinases are essential for venous constriction, arterial dilatation, and relaxation of arterial and trabecular smooth muscles, rigidity for penile erection (Rajfer J *et al*., 1992) (Trigo-Rocha F *et al*., 1994).

As PDE5 inhibitors are less effective due to their selective inhibition of phosphodiesterase's in penis rather than at their sites like vascular, visceral smooth muscles, platelets, cardiac muscles but not in cardiac myocytes. This makes PDE5 inhibitors more useful in men with comorbidities like men associated with cardiac diseases like ischemic heart diseases.

SIDE EFFECTS AND TOLERABILITY OF PED5 INIBITORS IN CARDIOVASCULAR DISEASE:

PDE5 inhibitors by class are known to initiate the release of nitric oxide and acetylcholine through cGMP hydrolysis at active sites. Thus, potentiating the effect of endogenous vasodilators like nitric oxide and acetylcholine and probably cause vasodilation. It is found that sildenafil decreases blood pressure by 10mmHg in healthy men (Jackson G *et al*., 1999) and probably have headache as a side effect due to its vasodilatory properties. But, predominant property of sildenafil is, it doesn't show any effect on pulmonary-caillary wedge pressure, heart rate or cardiac output and right atrial pressure. Thus, sildenafil is the safest drug for men with coronary artery disease (Hermann HC *et al*., 2000).

The most common adverse effects of tadalafil is headache and dyspepsia. Tadalafil does not cause any alterations in colour of vision unlike sildenafil (Padma-Nathan H *et al*., 2001).

In some cases myalgia and back pain are reported after administration of tadalafil with an moderate to severe pain in 12-24 hours after single use which usually resolves by itself or in more severe cases use of NSAID'S are recommended for relieving pain (Eli Lilly, 2001).

Safety and efficacy in men with benign prostatic hyperplasia:

a_1-adrenoreceptor antagonists are the drug of choice or subjects with benign prostatic hyperplasia. As in very common benign prostatic hyperplasia and ED coexist, the subjects are treated with phosphodiesterase inhibitors. But, a_1 adrenoreceptors antagonists are known to have a slight decrease in blood pressure hence an time interval of 4hrs is usually recommended between a_1-adrenoreceptor antagonists like terazosin, alfuzosin and tamsulosin and sildenafil use. Vardenafil are found to show an extreme fall in blood pressure when administered with terazosin. Hence, vardenafil is not recommender or can be used in exceptional conditions under monitoring of hypotension (kloner RA., 2004). Similarly, tadalafil is also known to lower the systolic and diastolic blood pressure, hence

sildenafil is safer when compared to other PDE5 inhibitors in combination with a_1-adrenoreceptor antagonist in subjects with benign prostatic hyperplasia (Kloner RA *et al*., 1999).

ED ASSOSCIATED WITH USE OF SERATONIN REUPTAKE INHIBITORS (PSYCHOGENIC ED) AND SPINAL CORD INJURY:

Studies have shown that the use of serotonin reuptake inhibitors in depression of 3 to 80% have lead to development of ED in elderly males. A retrospective study results have shown a recovery in ED in subjects with SSRI'S induced ED with the use of sildenafil (Rosen RC *et al*., 1999; Nurnberg HG *et al*., 2003; Nurnberg HG *et al*., 2001).

Parkinsonism is the other psychological disorder often seen with multiple system atrophy along with urinary and autonomic dysfunction. In Parkinson's disease with ED sildenafil is found to improve the erectile function with a stand by blood pressure of 90/50mmHg. Thus, in Parkinson's disease with multiple atrophy have its usual minimal effect, where as in parkinsonism associated with multiple system atrophy, sildenafil was found to cause orthostatic hypotension. Thus, sildenafil is contraindicated in parkinsonism with multiple system atrophy (Hussain IF *et al*., 2001).

Multiple Sclerosis and spinal cord injury in T6-L5 and spina bifida also results in ED (Palmer JS *et al*., 1999). In these subjects, the use of appropriate doses of sildenafil has improved the erectile function in cross sectional studies in about 80% of the subjects (Maytom MC *et al*., 1999).

NAION a reported effect of PDE5 inhibitors?

Non-arteritic anterior ischemic optic neuropathy is a sudden loss of eyesight reported in few patients after administration of sildenafil (Pomeranz HD *et al*.,2002), particularly in patients with pre-existing hypertension, diabetes, and hyperlipidemia with an age factor of 50 years. This is due to blockage of blood flow to optic nerves, probably associated with vascular insufficiency at the optic nerve head, leading to ischemia. FDA has reported the alarmed effects of sudden loss of eye sight using vardenafil, tadalafil and sildenafil in July 2005(anonymous 2). But, it is not clear which PDE5 inhibitors causes NAION, and it does not occur in all the men, only in complications like hypertension, diabetes, high cholesterol levels and hyperlipidemia and men over the age of 50yrs (Hattenhauer MG *et al*., 1997).

CONTRAINDICATIONS AND PRECAUTIONS:

As the PDE5 inhibitors act by releasing nitric oxide for relaxing the smooth muscles, other drugs containing or other forms of NO are contraindicated for concomitant use with PDE5 inhibitors, if taking with combination with nitrates they may result in hypotensive effects (Pfizer, 2010)(Wayne NJ & Bayer, 2011).

PDE5 inhibitors are contraindicated in patients with a known hypersensitivity to any components of the drugs. Avanafil has been reported for pruritis and eyelid swelling. Tadalafil and sildenafil are reported for NAION, Stenvens-johnson syndrome, exfoliative dermatitis and reared but serious hypersensitivity reactions (Eli Lilly, 2011).

Vardenafil ODT is contraindicated in patients with phenylketonuria as its formulation contains phenylalanine, and its sorbitol content makes it to have a caution in patients with fructose intolerance (Calif, 2012; Wayne Bayer NJ, 2011)

COMMENTS:

Sildenafil vs vardenafil:

Both sildenafil and vardenafil are short acting phosphodiesterase type 5 inhibitors with their short half life and rapid onset of action. However, sildenafil is more recommender to vardenafil in subject with comorbidities like ED with kidney transplant, ED with psychological disorders, ED with spinal cord injury, ED with diabetes and cardiovascular diseases and ED with benign prostatic hyperplasia due to its lower side effects and drug-drug interactions.

Sildenafil vs tadalafil:

Though sildenafil and tadalafil both fall under the class of PDE5 inhibitors, tadalafil has long duration of action than sildenafil thus, resulting in more number of erections in one use when compared to sildenafil.

NON-PHARMACOLOGICAL APPROACH FOR ED:

Due to alarming and unexpected side effect of allopathic medicines, now a day natural aphrodisiac potential are involved in the treatment of ED. This aphrodisiac potentials include biological sources like *Allium tuberosum, Eurycoma Longifolia, Crocus Sativus, Montanoa tomentosa, Myristica fragans:* (Myristcacecae), *Securidaca Longepedunculata, Boesenbergia Rotunda, Passiflora incarnate, Mondia whitei, Palisota Hirsuta* (Commelinacea), *Fadogia agrestis* (Rubiaceae), *Durio, Zibenthinus*, *Butea frondosa* (Papilionaceae), *Vanda tessellate*. Aphrodisiac plants act by inhibiting the hydrolyzing action of PDE-5 which hydrolyses cGMP which caeses erection. Thus, this prolongs the time for which blood gets trapped in the penis, thus maintaining erection firm enough for sexual intercourse (Sumalatha K,*et al*., 2010)

Other non-pharmacological treatment approaches for ED include sex tgerapy(Lizza EF, Rosen RC,1999.,) Vacuum Erection Device Therapy(Drogo K. Montague., 2002), Penile Prosthesis Implantation (Levine LA, Dimitriou RJ, 2001) Penile Vascular Surgery(Duncan JA., 1895)(Wooten JS.,1902., Lydston GF., 1908).

Adverse effects of vaccum erection therapy may includes decreased blood flow into the penis while the

tension band was in place, and decrease in penile skin temperature by about 1-degree C, cyanosia and congestion of extra corporeal tissue occurred (Nadig PW *et al*., 1986).

Contraindications of vacuum erection device therapy include patients using anticoagulants (Theiss M *et al*., 1995) and subjects with bleeding disorders. Caution is recommended in their concomitant use. Peyronie's disease (Ganem JP *et al*., 1998) or penile skin necrosis (Meinhardt W *et al*., 1990) and Fournier's gangrene (Kim JH & Carson CC, 1993; Limoge JP *et al*., 1996) are infrequently reported, but major complications of vacuum erection device therapy.

Figure 1. relaxation of smooth muscle via Nitric oxide–cGMP pathway (Corbin JD.,2004)

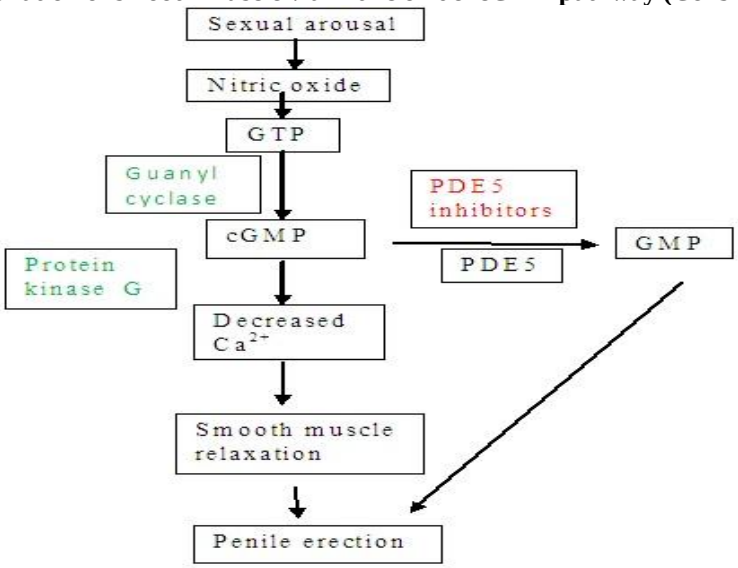

Table 1. Phosphodiesterase-5 (PDE_5) Inhibitors: Pharmacokinetic Summary:

	Sildenafil (Viagra)	**Vardenafil (Levitra)**	**Vardenafil ODT (Staxyn)**	**Tadalafil (Cialis)**	**Avanafil (Stendra)**
Bioavailability	41% (mean) 25%–63% (range)	15% (mean)	Not reported	Not reported	Not reported
T_{max}	1 hour (median) 0.5–2 hours (range)	1 hour (median) 0.5–2 hours (range)	1.5 hours (median) 0.75–2.5 hours (range)	2 hours (median) 0.5–6 hours (range)	0.5–0.75 hours(range)
Protein binding	96%	95%	95%	94%	99%
Metabolism	Major: CYP3A4 Minor: CYP2C9	Major: CYP3A4 Minor: CYP3A5, CYP2C	Major: CYP3A4 Minor: CYP3A5, CYP2C	CYP3A4	Major: CYP3A4 Minor: CYP2C
Active metabolite (% effect)	Yes (20%) *N*-desmethylation	Yes (7%) Desmethylation	Yes (7%) Desmethylation	No	Yes (4%) Methylation, glucuronidation
Half-life	4 hours	4–5 hours	4–6 hours	17.5 hours	5 hours
Elimination	80% feces 13% urine	91%–95% feces 2%–6% urine	91%–95% feces 2%–6% urine	61% feces 36% urine	62% feces 21% urine
Ingestion with high-fat meals	↓ C_{max} 29% ↑ T_{max} by 1 hour Avoid	↓ C_{max} 18%–50% May use (per manufacturer)	↓ C_{max} 35% May use (per manufacturer)	Not affected	↓ C_{max} 24-39% ↑ T_{max} by 1.12–1.25 hours May use (per manufacturer)

	Sildenafil (Viagra)	Vardenafil (Levitra)	Vardenafil ODT (Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Additional PDE inhibition	PDE_1, PDE_6	PDE_1, PDE_6	PDE_1, PDE_6	PDE_{11}	Not determined
ΔCmax with food	↓29%	Not determined	Not reorted	No change	Not determined
Onset of action	14-60min	25min	25-30min	16-45min	30-45min
Timing relative to intercourse	1hr	1hr	1hr	1-12hr	30min
AUC (μg/h/l)	1685 (100mg dose)	56.8 (20mg dose)	ND	8066 (20mg dose)	10867 (200mg dose)

C_{max} = peak concentration; CYP = cytochrome P450; ODT = oral dissolving tablet; Tmax = time to peak concentration.

CONCLUSION

All the three drugs sildenafil, vardenafil and tadalafil are similarly effective where sildenafil and vardenafil are short acting whereas tadalafil is a long acting drug. Before starting a therapy for ED one should merely assess the patient for the other comorbid conditions like benign prostatic hyperplasia, as phosphodiesterase inhibitors are contraindicated for concomitant use with a1-adrenoreceptor agonists and lead to lethal effects like postural hypotension. Sildenafil is only drug recommended in ED with benign prostatic hyperplasia with a window period of 4hrs.sildenafil is contraindicated in subjects with multiple system hypertrophy and concomitant use may cause hypotension. sildenafil is highly recommended in men with ED associated with cardiovascular disorders and multiple sclerosis. Thus, sildenafil is recommended over vardenafil and tadalafil on its safety and efficacy measures.

Major adverse effects like visual disturbances or sudden loss of eyesight or colour changes in vision are reported in use of sildenafil but not in particular with vardenafil and tadalafil. Vardenafil is almost similar to sildenafil. Tadalafil have minor adverse effects like headache and dyspepsia.

Besides pharmacological therapy there are many non-pharmacological therapies available for treating ED, but they are time consuming compared to pharmacological therapies, this makes patient to choose drugs like PDE5 inhibitors.

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Cite this article:
Pranathi Reddy R, Bhavani D, Aleem Sarwar. A Review On PDE-5 Inhibitors and Treatment Approaches Of Erectile Dysfunction.*International Journal of Pharmacy & Therapeutics*, 8(4), 2017, 153-159.
DOI: **http://dx.doi.org/10.21276/ijpt.2017.8.4.5**