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Avanafil: A Novel Agent for Management of Erectile Dysfunction, Its Clinical And Analytical Approach

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ABSTRACT

Erectile dysfunction is the sexual dysfunction characterized by inability to maintain an erection of penis during sexual performance. Oral phosphodiesterase type 5 inhibitors drugs are successful for treatment of impotence such as sildenafil, vardenafil, tadalafil, alprostadil and avanafil. Clinical trials reveals that avanafil have faster onset of action as well as higher specificity for phosphodiesterase type 5 inhibitors with fewer side effects in comparision of other oral phosphodiesterase type 5 inhibitors drugs. In case of analytical method only LC-MS/MS method has been done. There may be chances of analytical study of avanafil will be done in future by using various spectroscopy method.

Keywords: Avanafil, Erectile dysfunction, Clinical Study, Analytical Approach

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INTRODUCTION

Erectile dysfunction (ED), commonly known as 'impotence', is defined as the incapacity to attain or maintain a penile erection sufficient for successful vaginal intercourse[1]. ED is the medical disease that develops more commonly in elderly populations rather than the younger ones. Etiology behind ED is like advanced age, cardiovascular disorders, depression, low level of testosterone, drug abuse, psychological or psychiatric diseases and various drug related side effects. Now a days, various treatments are available for ED, such as psychotherapy, making lifestyle improvement, use of intraurethral medicated suppositories, taking phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, verdanafil and avanafil. All PDE5 inhibitors are used as first line medication in treatment of erectile dysfunction, however, avanafi have faster onset and higher specificity for phosphodiesterase type 5 inhibitor[2]. It has fewer side effects. During clinical trials, the data recommend that avanafil offer faster onset of action, well tolerated and successfully use in erectile dysfunction. In case of analytical method of avanafil, then only LC-MS/MS method has been done. Plasma concentration of avanafil has been estimated by this method. Except LC-MS/MS method, no any analytical method has been reported for avanafil. There may be chances of analytical study of avanafil will be done in future by using spectroscopy method such as UV, chromatographic method such as HPLC, Flourimetry etc.

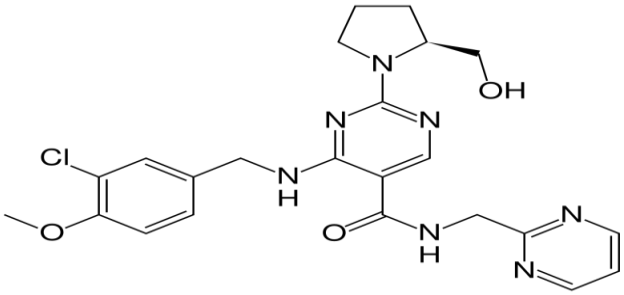

Figure 1: Structure of Avanafil

Erectile Dysfunction:

Erectile dysfunction is the common medical disease that primarily affects men older than 45 years of age. Erectile dysfunction is the regular or constant inability to sustain an erection of the penis sufficient to engage in sexual performance[3]. The most recent extensive analysis of published work on the prevalence of erectile dysfunction[4], on Definition/Epidemiology/Risk Factors for Sexual Dysfunction, showed that the prevalence of erectile dysfunction was 1–10% in men younger than 40 years. Prevalence of erectile dysfunction range from 2-9% in men between the ages of 40 and 49 years, it is then increases to 20–40% in men aged 60–69 years. In men older than 70 years, prevalence of erectile dysfunction ranges from 50-100%[5-9].

The physiology of penile erection involves release of NO (nitric oxide) in corpus carvenosum during sexual stimulation. NO then activate enzyme guanylate cyclase which increase level of cyclic guanosine monophosphate(cGMP) , which dilates the blood vessels in penis. This dilation of blood vessels allows increase entry of blood into penis which results in effective erection. Erectile dysfunction is now considered as a major health problem for the increasingly healthy ageing population. The main causes of erectile dysfunction include nerve or spinal cord damage, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome,atherosclerosis, depression, and lower urinary tract symptoms[10-16]. Several epidemiological studies shown that erectile dysfunction is indicator of cardiovascular disease (CVD) [9,12,14] . Findings from other studies have reported that certain environmental and lifestyle factors, such as smoking, obesity, and limited or an absence of physical exercise, might also be important predictors of erectile dysfunction[17-19]. Other causes include hormonal disease, alcoholism, performance anxiety, sexual aversion and drugs like anti cancer, cocain, narcotics, sedatives. In several studies, an extensive alteration of lifestyle habits, through modification of diet and encouragement to exercise, led to improvement of erectile dysfunction[20-24]. In addition, the phosphodiesterase type 5 inhibitor drugs such as sildenafil, tadalafil, verdanafil and avanafil which are also use in treatment of erectile dysfunction. Some natural therapy like L-Arginine, gingko, ashwagandha, yohombine can impair erectile dysfunction.

Avanafil:

Avanafil is a newly invenstigational remedy for curing erectile dysfunction or impotence by Vivus, Inc (biopharmaceutical company).It was granted by US Food and Drug Administrationon on April 27, 2012[26]. Stendra is the brand name of avanafil which got licence from Mitsubishi Tanabe Pharma Corporation. It is also approved in South Korea and sold under the brand name of Zepeed by JW Pharma.

Avanafil is chemically known as (S)-4-[(3-Chloro-4-methoxybenzyl)-amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2pyrimidinylmethyl)-5-pyrimidinecarboxamide has empirical formula of $C_{23}H_{26}ClN_7O$ and molecular weight 483.95gm/mol. It is derivative of pyrimidine and the synthesis of avanafil consists of series of displacement reactions[27].

Avanafil is a white crystalline powder and the USP recommends that it should be stored at 20°C to 25°C, in air tight containers and protected from light. It is slightly soluble in ethanol, neutral buffer and alkaline buffer, practically insoluble in water and soluble in 0.01 mol/L hydrochloric acid, methanol and acidic buffer[28]. It has pKa value around 4. The melting point and density of

avanafil is 150-152 ^{o}C, 1.372 g/cm3 respectively. Sexual stimulation causes release of nitric oxide in the corpus cavernosum, nitric oxide then activates the enzyme guanylate cyclase, which in turn enhances the cGMP levels, increase in cGMP levels cause smooth muscle relaxation. Phosphodiesterase type 5 inhibitors like avanafil increase the effects of nitric oxide and causes smooth muscle relaxation of the corpus cavernosum by inhibiting the degradation of cGMP. Avanafil Extensively metabolized by CYP3A4 enzyme and to a minor extent by CYP2C isoform. Major circulating metabolites are M4 and M16 and are about 23% and 29% that of the parent compound, respectively. The peak plasma time is 30 – 45 min and protein binding of drug is 99%. It is excreted as metabolites, mainly in the feces (approximately 62%) and to a lesser extent in the urine (approximately 21%). It is mainly contraindicated with any form of organic nitrates.Avanafil is also mentioned as 'Son of Viagra'. Avanafil is quite chemically similar to sildenafil but sildenafil has reported extreme side effects. Other orally administered PDE5 inhobitors are sildenafil, udenafil, microdenafil, verdenafil and tadalafil and their characteristics are as given table.

Table 1: Erectile Dysfunction Treatment[25]

Class	**PDE5 Inhibitor**				**Prostaglandine E1**		**α_2-Blocker**
Drugs	Avanafil	Tadalafil	Sildenafil	Verdenafil	Alprostadil		Yohimbine
Brand	Stendra	Cialis	Viagra	Levitra	Muse	Caverject	Yokon
Company	Vivus	Lilly Icos	Pfizer	Bayer & GSK	Vivus	Pfizer	Glanwood
Dose	50mg 100mg 200mg 500mg	2.5mg, 5mg 10mg 20mg	25mg, 50mg, 100mg	2.5mg, 5mg 10mg 20mg	125mcg 250mcg 500mcg 1000mcg	5mcg 10mcg 20mcg 40mcg	5.4mg
Dosage form	Tablet	Tablet	Tablet	Tablet	Supposito y	Injection Intravenous	Tablet
Duration of action	36 – 48 hr	36 hr	4 hr	4 hr	0.5 – 1 hr	1 hr	-
Onset of action	15 min	2 hr	1 hr	1 hr	5 – 10 min	5 – 20 min	-

Table 2: Characteristics of PDE5 Inhobitors[29-35]:

Drugs	**On set of action**	**Duration of action**	**Efficacy**	**Food & alcohol interaction**	**Contraindication**
Sildenafil	30-60 min	4-8 hr	>65%	Administer while fasting because interact with food, No alcohol interaction	Nitrate-containing compounds, serious cardiovascular disease, non-arteritic ischaemic optic neuropathy, and α blockers
Udenafil	30-60 min	12 hr	>65%	No alcohol	Nitrate-containing

				interaction	compounds, serious cardiovascular disease, non-arteritic ischaemic optic neuropathy, and α blockers
Microdenafil	30-60 min	6-12 hr	>65%	No food or alcohol interaction	Nitrate-containing compounds, serious cardiovascular disease, non-arteritic ischaemic optic neuropathy, and α blockers
Verdenafil	30 min	4-8 hr	>65%	Administer while fasting because interact with food, No alcohol interaction	As for sildenafi, but also type 1 or 3 antiarrythmics and congenital prolonged QT syndrome
Tadalafil	45 min	Up to 36 hr	>65%	No food or alcohol interaction	Nitrate-containing compounds, serious cardiovascular disease, non-arteritic ischaemic optic neuropathy, and α blockers
Avanafil	15 min	36-48 hr	>65%	No food interaction, Interact with alcohol	Any form of organic nitrates and hypersensitivity patients

Table 3: Mean Change in Baseline for the Primary Efficacy Variables usually ED Population (Study 1)[36]

Quantity of drug	**Placebo (N=155)**	**Stendra 50 mg (N=154)**	**Stendra 100 mg (N=157)**	**Stendra 200 mg (N=156)**
IIEF EF Domain Score				
Endpoint	15.3	18.1	20.3	22.2
Change from baseline$^{\diamond}$	2.9	5.4	8.9	9.5
p-value*	-	0.0014	<0.0001	<0.0001
Vaginal Penetration (SEP2)				
Endpoint	53.8%	64.3%	73.9%	77.3%
Change from baseline$^{\diamond}$	7.1%	18.2%	27.2%	29.8%
p-value*	-	0.0009	<0.0001	<0.0001
Successful Intercourse (SEP3)				
Endpoint	27.0%	41.3%	57.1%	57.0%
Change from baseline$^{\diamond}$	14.1%	27.8%	43.4%	44.2%
p-value*	-	0.0002	<0.0001	<0.0001

$^{\diamond}$ Least-square estimate from ANCOVA model

* comparison to placebo for vary from baseline

Table 4: Mean Change from Baseline for the Primary Efficacy Variables in ED Population with Diabetes Mellitus (Study 2)[36]

Quantity of drug	Placebo N=127)	Stendra 100 mg (N=126)	Stendra 200 mg (N=126)
IIEF EF Domain Score			
Endpoint	13.2	15.8	17.3
Change from baseline$^{\diamond}$	1.8	4.5	5.4
p-value*	-	0.0017	<0.0001
Vaginal Penetration (SEP2)			
Endpoint	42.0%	54.0%	63.5%
Change from baseline$^{\diamond}$	7.5%	21.5%	25.9%
p-value*	-	0.0004	<0.0001
Successful Intercourse (SEP3)			
Endpoint	20.5%	34.4%	40.0%
Change from baseline$^{\diamond}$	13.6%	28.7%	34.0%
p-value*	-	<0.0001	<0.0001

$^{\diamond}$ least-square estimate from ANCOVA model

* Comparison to placebo for differ from baseline

Avanafil and its Clinical Approach:

Clinical trials conducted for assessing effect of Avanafil. STENDRA was detected in three randomized, double-blinded, placebo-controlled, group trials for 3 months. In these 3 trials, STENDRA was taken at doses of 50 mg, 100 mg, and 200 mg. Prior to initiation of sexual activity , patients took 1 dose of study drug approximately 30 minutes. Alcohol and food intake was not restricted. In addition to this, the subset of patients from 2 of these trials was engaged into an open trial. In the open-label extension trial, patients were initially allowed to take avanafil 100 mg. During the trial, at any stage patients should increased the dose of avanafil to 200 mg or decreased dose to 50 mg which based on their individual response to the treatment. The three primary outcome find Sexual Encounter Profile (SEP) and the erectile function domain of the International Index of Erectile Function (IIEF). The IIEF was taken at the baseline and at 4-week intervals during the treatment. It has a 30-point score, where the higher scores observe better erectile function. Patients observed data regarding each sexual effort made during the trial. Finally results are shown from the diabetic population with ED (Study 2) and the other in the general ED population (Study 1)[36].

Results in General ED Population (Study 1):

STENDRA was tested in 646 men with ED of various etiologies. The mean age was 55.7 years

(range from 23 to 88 years). The mean duration of ED was 6.5 years. STENDRA at the doses of 50 mg, 100 mg and 200 mg shows significant improvement in all the 3 primary efficacy variables relative to placebo[36].

Results in ED Population with Diabetes Mellitus (Study 2)

STENDRA was evaluated at fixed dose for trial up to 3 months in ED patients (n=390) with type 1 or type 2 diabetes mellitus in a double-blinded, randomized, parallel, placebo-controlled, tablet was evaluated at fixed dose for trial up to 3 months. The average age was 58 years. The mean duration of the ED was 6 years. In this trial, tablet (Stendra) at doses of 100 mg and 200 mg shown significant improvement in all the 3 primary efficacy variables as detected by the IIEF questionnaire; SEP2 and SEP3[36]. From the clinical data it revales that avanafil have faster onset of action approximately 15 min and longer duration of action 36-48 hr than any other PDE5 inhibitor. Avanafil is highly selective medication with lesser side effects.

Preclinical studies have shown that Avanafil very strongly inhibits PDE5 in a competitive manner. Also, Avanafil has higher selectivity against PDE6 and PDE1 than Sildenafil and Vardenafi. Avanafil was generally well tolerated at doses of 50 to 200 mg per day for 7 days. All adverse events were mild, and no treatment was required. So it is most effective PDE5 Inhibitor drug. Avanafil has onset of action approximately 15 min and duration of action 36-48 hr. Avanafil is highly selective medication with lesser side effects.

Avanafil and its Analytical Approach:

Avanafil is the latest drug for the treatment of erectile dysfunction since; no analytical method has been reported for its estimation except LC- MS/MS. It has been used in determination of Avanafil plasma concentrations which was conducted at the Asian Medical Center Analytic Laboratory. Plasma concentrations of avanafil were measured by a sensitive and selective method by using online solid-phase extraction (SPE) coupled to LC-MS/MS; a triple quadrupole mass spectrometer was also used. Stock solutions of the avanafil and the Internal standard (IS [TA-179013C5 15N1 d2]) were prepared by dissolving 1 ng/mL of each in methanol. Twenty microliters of IS was added to each 200-µL aliquot of plasma, and the sample was transferred to an auto sampler vial, which was put into the online SPE (Symbiosis; Spark Holland B.V., Emmen, the Netherlands) and LC-MS/MS system (API 4000; Applied Biosystems/MDX Sciex, Toronto, Ontario, Canada). Chromatographic separation was conducted using the C18 column (Capcell Pak; Shiseido Co. Ltd., Tokyo, Japan; particle size, 3 µm; internal diameter, 2.0 × 50 mm). The mobile phase was the mixture of 10-mM ammonium format (pH 2.5) and acetonitrile

(v/v 65:35), with a flow rate of 0.3 mL/min and a column temperature of 30°C. The chromatographic run time was the 5 minutes, and injection volume was selected to 5 µL. The mass spectrometer with the electrospray ionization source was operated in the positive mode. Quantitation was conducted using multiple reactions monitoring of transitions of m/z 484.1 → 375.1 for avanafil and m/z 492.3 → 383.2 for IS. Avanafil concentrations were calculated from avanafil calibration curves, which were obtained by plotting the peak height ratio versus the concentration of avanafil[37].

CONCLUSION:

Avanafil is recently approved newer medicine in phosphodiesterase type 5 inhibitor class. The response time between taking a tablet and experiencing the effect is extremely fast for avanafil, so from the clinical data it revales that avanafil has faster onset of action and longer duration with fewer drawbacks than any other PDE5 inhibitor. In analytical field, there may be various chances for doing research work on avanafil in its bulk formulation by using many spectroscopic methods like UV, Flourimetry, Chromatigraphic method like HPLC, Gas chromatography and Mass spectrometry.

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