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Chronic Daily Administration of Vardenafil in Erectile Dysfunction Patients Has No Impact on Semen Parameters or on Sex Hormones Levels

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Abstract: Objective: To study the potential impact of vardenafil when given in a daily dose on the semen parameters and sex hormones levels of erectile dysfunction (ED) patients. Setting: Andrology Clinic - Dr. Ahmad Fikry Medical Centre, Abu Dhabi, United Arab Emirates. Patients: Forty male subjects complaining of erectile dysfunction were enrolled in the study from November 2007 - May 2008. Intervention: All recruited subjects were subjected to semen analysis and measurement of sex hormones levels that is done before and then after 4 months of continuous daily use of vardenafil 20 mg in the first group or placebo in the second group. Results: No statistically significant differences were observed in the seminal parameters or in the hormonal levels in ED patients done before and after vardenafil therapy. Conclusions: Vardenafil is largely a safe new medication for erectile dysfunction that has no serious impact on neither seminal parameters nor sex hormonal levels of treated patients.

Key words: Vardenafil, Erectile Dysfunction, seminal and Hormonal Levels

INTRODUCTION

Erectile dysfunction (ED) is a common condition that is associated with increasing age and the presence of many medical conditions, including cardiovascular disease and diabetes mellitus (Hedelin H. and P. Stroberg, 2005). Although other manage-ment options are now available, oral pharmacotherapy with a phosphor-diesterase type 5 (PDE5) inhibitor is currently the first choice of most physicians and patients for the treatment of ED (Mulhall J.P. and F. Montorsi, 2006).

Currently, there are three PDE5 inhibitors available, namely sildenafil, vardenafil and tadalafil, and all have demonstrated efficacy and tolerability in a wide range of ED populations (Goldstein I., J.M. Young, *et al,* 2003). Vardenafil is a PDE5 inhibitor that induces cGMP accumulation in human Corpus cavernosum, thus potentiating NO-induced penile erection in ED men (Porst H., R. Rosen, N.H. Padma, *et al,* 2001). As with other PDE5 inhibitors, vardenafil is taken on demand before commencing the sexual act (Stief C., H. Porst, 2004), but little is known about its use on daily basis in ED men nowadays and its effects on their body functions with this new regimen.

The aim of the present study is to inverstigate whether the daily dosing of vardenafil in ED patients could possibly has any potential serious effect on seminal parameters as well as sex hormonal levels of those ED patients treated.

MATERIALS AND METHODS

Fourty male subjects complaining of erectile dysfunction were selected from Andrology Clinic, Ahmad Fikry Medical Centre, Abu Dhabi, United Arab Emirates. The study covered the period from November 2007 - May 2008. All selected subjects gave written consent for participation in the study. All ED patients had a score < 20 (Table 1) on the erectile function (EF) domain score of the International Index of Erectile Function (IIEF) calculated as the sum of scores from questions 1-5 and 15. The following were done for all the patients:

1. Detailed medical and sexual history.
2. Thorough medical examination.
3. Duplex study of the cavernosal arteries.

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The recruited subjects were divided into two major groups:

- Group one comprising twenty men who received vardenafil 20 mg tabs. daily for 4 months.
- Group two comprising twenty men who received a placebo daily for 4 months.

Table 1: showing baseline patient demographics.

Parameters	Placebo (N-20)	Vardenafil (N=20)
Mean age, years	53.2	54.1
Mean BMI, Kg/m^2	26.9	26.2
Mean duration since ED diagnosis made, years	3.2	2.9
Mean baseline IIEF-EF score	15.3	14.9
Comorbid conditions, %		
Hypertension	40	50
Diabetes	25	30
Hyperlipidemia	20	20
Aetiology of ED, %		
Organic	25	27
Psychogenic	23	20
Mixed	52	53

The ED patients were selected according to the following inclusion criteria:

- Gave a history of ED during the past 6 months.
- Age ranges from 18-60 ys.
- Indulged in a stable heterosexual relationship at least for the past 6 months.
- History of current use of PDE5 inhibitors or any ED therapy is negative for the past 3 months.
- Compliant cooperative patient with fairly stable personality, who can afford vardenafil daily.

The following exclusion criteria were strictly applied throughout the study:

- Patients with history of unstable angina, myocardial infarction, congestive heart failure, serious and/or uncontrolled arrhythmias or stroke during the past 6 months.
- Patients with chronic liver disease for the past 6 months or abnormal liver functions.
- Patients with persistently high serum creatinine >2.0 mg/dl.
- Patients with abnormal thyroid function whether hypo- or hyperthyroidism.
- Patients with uncontrolled diabetes.
- Patients with clinically or serologically demonstrable haematological disease.
- Patients with moderate-severe penile anatomical abnormalities that significantly interfere with erection.
- Patients with retinitis pigmentosa or other inherited eye diseases.
- Patients using androgens, anti-androgens, anti-coagulants or anti-depressants for the past 3 months, patients under nitrate therapy.
- Patients receiving medications that interfere with cytochrome CYP 450 3A4.
- Patients having serum total testosterone >10% below lower limit of normal.
- Patients with unstable psychiatric condition or on substance abuse and/or addiction.

For both groups, semen analysis and measurement of sex hormones levels were done before and at the end of the study.

Seman analysis was processed according to the WHO guidelines with abstinence period of 48 hrs., using the masturbation technique, collected at a special room and immediately delivered to the lab. Sex hormones levels namely LH, FSH and testosterone were measured using Eliza technique (Mini Vidas, BioMérieux, Italy). The normal range for LH and FSH accepted was 1-10 IU/ml while that for testosterone was 3-10.6 ng/ml.

All the results were analysed using windows SPSS version 10 employing paired-t-test and independent t-test.

RESULTS AND DISCUSSION

Erectile dysfunction is a frequent age-related disorder resulting from a combination of organic and psychologic factors (Saenz de Tejada I., J. Angulo, *et al*, 2005). Erectile dysfunction has a profound effect on man's sense of self and quality of life. Men also report that ED affects not only the emotional intimacy in their primary relationship, but also their daily interactions with women or other potential partners (Latini D.M., D.F. Penson, *et al*, 2002). It has been estimated that ED currently affects 152 million men worldwide, and this number is estimated to reach 322 million by 2025 (Ayta I.A., *et al,* 1999).

With the revolutionary introduction of oral therapy (sildenafil, the first PDE5 inhibitor) for ED at the end of the previous decade, a safe and effective treatment, in many ways mimicking natural erection became available (Gonzalgo M.L., M. Brotzman, *et al,* 2003). This has led to an increasing number of patients seeking treatment for their ED (Fisher W.A., R.C. Rosen, 2004).

Vardenafil (levitra®) is the latest member of the PDE5 inhibitors family released at the market just few years after launching of its first pioneer product, namely sildenafil citrate. Vardenafil is a potent and highly selective PDE5 inhibitor. Vardenafil improved erectile function in men with mild to severe ED of varying aetiology and it is generally well tolerated with few side effects that are typical of PDE5 inhibitors although they are mild to moderate in intensity and transient in nature (Edwards D., Hackett, 2006; Padma-Nathan H., 2007; Tan H.M., C.M. Chin, 2008).

Phosphodiesterase 5 catalyses the breakdown of cGMP which is the most abundant second messenger in the human Corpus cavernosum. By hydrolyzing the phosphodiesterase bond of cGMP, cGMP is converted into the biologically-inactive monophosphate, resulting in termination of its physiologic function (Küthe A., *et al,* 2001) Vardenafil as a highly selective PDE5 inhibitor blocks previous step resulting in accumulation of cGMP that fascilitates and potentiates relaxation of cavernosal and vascular smooth muscle cells, thus eventually terminating with satisfactory penile erection (Corbin J.D., 2004).

Vardenafil like other members of its group is given on-demand basis mainly i.e. the patient receives his dose whenever he decides to have sexual relation with his partner.

Vardenafil works as early as 11 minutes after intake with extended efficacy up to 8 h. postdose (Montorsi F., H. Padma-Nathan, 2004).

Having stated that, daily dosing of PDD5 inhibitors at bed time became a successful treatment option in early sexual rehabilitation of patients after nerve-sparing radical prostatectomy (NSRP) (Schwartz E.J., P. Wong, 2004). Later on, daily dosing with PDE5 inhibitors turned out to be very successful in non-responders to on-demand treatment (McMahon C., 2004).

Although this was proven true for sildenafil and tadalafil, it certainly can be assumed that this also holds true for all PDE5 inhibitors including vardenafil, in particular in patients with severe organic ED (Hartmut Port, 2006).

In the current study, 40 ED patients were classified to receive either daily dosing with vardenafil 20 mg or placebo for 4 consecutive months.

For the assumed effect of chronic daily dosing of vardenafil on seminal parameters namely sperm count, motility and percentage of abnormal morphology, no statistically significant difference was found between predose and postdose measurements for vardenafil group as shown in Table (2).

Table 2: showing that for both vardenafil and placebo groups, comparing the pretest and posttest values of seminal parameters and sex hormonal levels are statistically insignificant (P>0.05) using paired- t test.

Parameters		Paired Differences			95% Confidence interval of the Difference		t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	E.D. Var Before (Sp Conc) -E.D. Var After (Sp Conc)	-5750	1.8728	.4188	-1.4515	.315	-1.373	19	.186
Pair 2	E.D. PI Before (Sp Conc) – E.D. PI After (Sp Conc)	-.9550	1.9720	.4410	-1.8779	-.21E-02	-2.166	19	0.073
Pair 3	E.D. Var Before (Sp Mot)– E.D. Var After (Sp Mot)	8.500E-03	4.416E-02	9.875E-03	-1.22E-02	2.917E-02	.861	19	400
Pair 4	E.D. PI Before (Sp Mot)- E.D. PI After (Sp Mot)	4.150E-02	.1594	3.565E-03	-3.31E-02	.1161	1.164	19	0259
Pair 5	E.D. Var Before (Ab Sp)- E.D. Var After (Ab Sp)	-1.05E-02	1.605E-02	3.589E-03	-1.80E-02	2.99E-03	-2.926	19	0.259
Pair 6	E.D. PI Before (Ab Sp)- E.D. PI After (Ab Sp)	-4.00E-03	1.635E-02	3.656E-03	-1.17E-02	3.653E-03	-1.094	19	.288
Pair 7	E.D. Var Before (LH)-E.D. Var Af ter (LH)	2.3800	10.6443	2.3801	-2.6017	7.3617	1.000	19	.330
Pair 8	E.D. PI Before (LH)-E.D. PI After (LH)	-2.00E-02	.1196	2.675E-02	-7.60E-02	3.600E-02	-.748	19	.464
Pair 9	E.D. Var Before (FSH)- E.D. Var After (FSH)	1.8150	18.6662	4.1739	-6.9210	10.5510	.435	19	.669
Pair 10	E.D. PI Before (FSH)-E.D. PI After (PSH)	-1.50E-02	.1137	2.542E-02	-6.82E-02	3.820E-02	-.590	19	.562
Pair 11	E.D. Var Before (Testo)- E.D. Var After (Testo)	-.2100	.9668	.2162	-.6625	.2425	-.971	19	.344
Pair 12	E.D. PI Before (Testo)- E.D. PI After (Testo)	-2.50E-02	.1251	2.798E-02	-8.36E-02	3.356E-02	-.893	19	.383

Regarding the assumed effect of chronic daily dosing of vardenafil on sex hormonal levels namely LH, FSH and testosterone. Again, no statistically significant difference was found between predose and postdose measurements in the vardenafil group as shown in Table (2).

Also, comparing the predose and postdose measurements of both vardenafil and placebo groups does not reveal any statistically significant difference in connection with seminal parameters or with sex hormonal levels as shown in Table (3).

Table 3: Showing that comparing the mean values of pretest and posttest measurements of vardenafil group versus placebo group are statistically insignificant (P>0.05) using independent t-test.

Parameters	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Differ-ence	Std. Error Differ-ence	95% Confidence Interval of the Difference	
								Lower	Upper
SP Conc Before									
Equal variances Assumed	.778	.383	1.273	38	.211	11.1300	8.7452	-6.573	28.8337
Equal variances not assumed			1.273	37.112	..211	11.1300	8.7452	-6.5876	28.8476
SP Conc After									
Equal variances Assumed	.638	.429	1.213	38	.232	10.7500	8.8593	-7.1848	28.6848
Equal variances not assumed			1.213	37.249	.233	10.7500	8.8593	7.1967	28.6967
SP Mot Before									
Equal variances Assumed	1.533	.223	-.498	38	.621	-3.7000E-02	7.430E-02	-.1874	.1134
Equal variances not assumed			-.498	3.384	.622	-3.7000E-02	7.430E-02	-.1876	.1136
SP Mot After									
Equal variances Assumed	2.355	.133	-0.59	38	.953	-4.0000E-03	6.748E-02	-.1406	.1326
Equal variances not assumed			-0.59	35.879	.953	-4.0000E-03	6.748E-02	-.1409	.1329
Ab Sp Before									
Equal variances Assumed	3.266	.079	-1.704	38	.096	-.1160	6.806E-02	-.2538	2.177E-02
Equal variances not assumed			-1.704	34.054	.097	-.1160	6.806E-02	-.2543	2.230E-02
Ab Sp After									
Equal variances Assumed	2.542	.119	-1.602	38	.118-.1095	6.837E-02	-.2479	2.890E-02	
Equal variances not assumed			-1.602	34.762	.118	-.1095	6.837E-02	-.2483	2.932E-02
LH Before									
Equal variances Assumed	1.691	.201	.661	38	.5121.6800	2.5404	-3.4628	6.8228	
Equal variances not assumed			.661	20.586	.516	1.6800	2.5404	-3.6096	6.9696
LH After									
Equal variances Assumed	.945	.337	-1.103	38	.227	-.7200	.6528	-2.0414	.6014
Equal variances not assumed			-1.103	36.575	.277	-.7200	.6528	-2.0431	.6031
PSH Before									
Equal variances Assumed	3.263	.079	1.042	38	.304	3.6850	3.5374	-3.4760	10.8460
Equal variances not assumed			1.042	19.815	.310	3.6850	3.5374	-3.6982	11.0682
PSH After									
Equal variances Assumed	1.555	.220	.761	38	.452	1.8550	2.4386	-3.0817	6.7917
Equal variances not assumed			.761	20.803	.455	1.8550	2.4386	-3.2193	6.9293

Table 3: Continued.

Testo Before									
Equal variances Assumed	.052	.820	-.794	38	.432	-.5350	.6742	-1.8999	.8299
Equal variances not assumed			-.794	37.968	.432	-.5350	.6742	-1.8999	.8299
Testo After									
Equal variances Assumed	1.063	.309	-5.68	38	.573	-.3500	.6159	-1.5968	.8968
Equal variances not assumed			-.568	35.848	.573	-.3500	.6159	-1.5993	.8993

Our results are in agreement with that of Jarvi *et al.* (2008) who found that vardenafil given as 20 mg daily has no noticeable effect on semen parameters or on reproductive hormones when compared with placebo. We believe that daily nightly dosing with vardenafil would become the mainstay in the future for the treatment of ED patients especially those with severe organic ED and non-responders to the usual on-demand PDE5 inhibitor dosage even when given at the maximum therapeutic dose. On the contrary, some recent studies have demonstrated that daily vardenafil has comparable efficacy to on-demand regimen (Montorsi F., G. Brock, J. Lee, *et al,* 2008; Zumbé J., H. Porst, 2008). We do believe that such point needs further detailed studies as the first study focused on NSRP-induced ED men only while the second study focused on men with mild-moderate ED only and both studies did not include more difficult-to-treat organic ED or mixed-aetiology cases. Besides, chronic dosing with PDE5 inhibitors resulted in improvement of endothelial dysfunction. This holds true not only for the cavernous bodies, but also for the endothelium of the whole vascular system (Behr-Roussel D., D. Gorny, 2008; Behr-Roussel D., D. Gorny, 2005).

Conclusions:

Vardenafil is a potent and highly selective PDE5 inhibitor. It is largely a safe drug when given in chronic daily dosing with no demonstrable effects on ED men regarding their seminal parameters or their sex hormonal profile. Such findings may open a new frontier in the treatment of severe ED cases in the era of PDE5 inhibitors.

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