Post Ejaculatory Effects of Sildenafil Citrate (Viagra) On Sexual Responses In Diabetic Neuropathic Men

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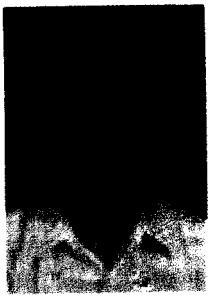

Abstract:

Background: Erectile dysfunctions in diabetes are important signs probably due to pelvic autonomic neuropathy with damage to the parasympathetic nervierignetes. Direct evidence for a neuropathic etiology comes from studies that show structural changes in autonomic nerve fibers supplying the corpora cavernosa.

The present study deals with the post ejaculatory effects of sildenafil citrate (Viagra) administration on sexual dysfunctions associated with diabetic neuropathy/ erectile impotence prevailing in the male population.

Aim: To investigate whether sildenafil citrate administration maintains improved erectile functions in diabetic men with established autonomic neuropathy during post ejaculatory refractory phase (the phase of re-obtaining erection after ejaculation) after psychic and physical sexual stimulation. These findings may be of patho-physiological significance for the use of sildenafil citrate on the management of erectile dysfunctions in diabetic neuropathic men.

Methods: The study design consisted of a prospective cross-over, two period investigation (Pre and post ejaculation before and after the intake of 50 mg Viagra). Eectile/sexual functions including libido, erection frquency, masturbation ability, pattern of ejaculation, and pattern of erection lost were noted during audiovisual sexual stimulation in 50 insulin dependent diabetes mellitus (IDDM) and in 50 non insulin dependent diabetes mellitus (NIDDM) patients with and without an objective evidence of neuropathy, having an age span in between 20 and 65 years and a duration of diabetes distributed over 1-25 years with their age matched non diabetic controls.

Results: Sildenafil treatment showed a significant improvement ($P<0.0005$ in some cases) in all the parameters during the first ejaculatory phase in both types of diabetic neuropathics and were found to be maintained (absolute) during post-ejaculatory phase as well. However, this difference was found to be non significant in both types of diabetic patients without neuropathy and when compared with their respective control subjects during the first ejaculatory phase. A complete failure in the pattern of erotic responses in these subjects during the post ejaculatory phase was also observed since no erection/ejaculation could be achieved during this phase.

Conclusion: These results suggest that sildenafil citrate is an effective and well-tolerated treatment for erectile/sexual dysfunction in patients with diabetic neuropathy and has a positive influence over the resumption of erections and sexual functions following post ejaculation in the presence of a continuous psycho-sexual stimulus and adds a new aspect of interest in the research area concerning the regulatory mechanism of male copulatory behaviour.

Key-Words: Diabetic neuropathy, Sildenafil citrate, Post ejaculatiory sexual behavior

Introduction:

Erectile dysfunction is a common multifactorial complication of diabetes mellitus. Long term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. Direct evidence for a neuropathic etiology of diabetic erectile dysfunction comes from studies that show structural changes in autonomic nerve fibers supplying the corpora cavernosa[1]. Emission disturbances that occur in diabetes are associated with involvement of the sympathetic fibers that sub serve the seminal vesicles, vas deferens, and bladder[2]

Testicular anesthesia, presence of a neurogenic bladder, and delayed bulbocavernous reflex response latency are indirect evidence for a neuropathic etiology of the patient's complaints[3]. Failure of ejaculation secondary to emission disturbances due to sympathetic denervation of the vas deferens is another manifestation of autonomic neuropathy, usually seen in more advanced stages[4,5]. It is now established that sexual dysfunction is a common complication of diabetic autonomic neuropathy both in men and in women[6,7,8,9]. Despite the general agreement of previous investigators that the prevalence of impotence in diabetic men approximates 50 per cent, there is controversy surrounding the etiology of this problem. and the pathologic basis of diabetic autonomic neuropathy is still incompletely understood.

Numerious strategies have been tried to overcome this diabetic complication including improvin glycaemic control, drugs that influence penile rigidity, vacuum assisted devices to produce an erection-like state, operations to apply prostheses within the penis and psychological councseling.

One interesting new breakthrough in the treatment of erectile dysfunctions using oral drugs lies in the substance sildenafil citrate (*Viagra*^{TM}) seems to be a most promising discovery[10].

Sildenafil is a potent and selective inhibitor of the cyclic guanosine monophosphate (cGMP)-

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specific phosphodiesterase type 5 (PDE5), which is responsible for the degradation of cGMP in the corpus cavernosum[11,12].

Sildenafil has a peripheral site of action on erections. It potently enhances the relaxant effect of nitric oxide (NO) on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Increased levels of cGMP are involved in smooth muscle relaxation, which in turn leads to penile erection. cGMP is converted back to guanosine monophosphate (GMP), a cGMP precursor, by the action of phosphodiesterase type 5 (PDE5). Sildenafil prevents the breakdown of cGMP thereby preventing premature detumescence. Furthermore, treatment with sildenafil is well tolerated and is associated with minimal adverse events that rarely cause discontinuation of the treatment[13].

The effectiveness of sildenafil in patients with various etiologies has been confirmed in a large fixed dose study where the 514 men had erectile dysfunction that was organic in 32%, psychogenic in 25% and mixed in 43%[14]. In a follow-up of 267 patients, there was a corellation between baseline sexual function and response to sildenafil, but even in patients with severe erectile dysfunction there is a 41% satisfaction rate[11]. There are also lower rates of satisfaction with sildenafil in patients with neurogenic cause of erectile dysfunction (diabetic neuropathy) than psychogenic or vasculogenic erectile dysfunction[15]. Recently, sildenafil has been shown to restore erections in temporary erectile dysfunction related to the need of semen collection for assisted reproductive techniques through its ability to to reduce post-ejaculatory refractory time in the presence of a continous erotic stimulus. This adds a new aspect of interest in the reseach area concerning the regulatory mechanisms of male copulatory behavior[16].

In the present investigation we have defined our main outcome measure whether sildenafil citrate's prolong ejaculatory latency and shorten refractory period is beneficial for the achievement of penile rigidity satisfactory penetration and sufficiently prolonged to enable sexual intercourse to be completed in diabetic neuropathic men.

Materials and Methods

This research was conducted in the department of physiology, faculty of Medicine, Umm-al-Qura university Makkah, during the academic year 2006-2007. Subjects were all resident of the city of Makkah and the surrounding vicinity, Saudi Arabia. For experimental purposes and for the studies of diabetic neuropathy, after getting the permission from the local ethical committee, 50 diabetic men both insulin dependent (IDDM) and non insulin dependent (NIDDM) with and without evidence of neuropathy and 50 age matched non diabetic male controls were selected. Every male aged between 20 to 65 years with duration of the onset of the disease to 1 to 25 years was included.

The presence of diabetic complications were assessed by a review of the medical record. Neuropathy was present if the records indicated absence of ankle jerk, decreased vibration sense or pin prick sensation in the feet or hands, or there was history of neuropathic pain, foot ulcer, or symptoms compatible with autonomic neuropathy (differential diagnosis) including postural hypotension, intermittent diarrhea especially nocturnally, epigastric fullness, bladder dysfunction, diminished sweating in the legs, gustatory sweating and hypoglycemic unawareness. The criteria for the presence of symptomatic autonomic neuropathy were two or more severe or three or more mild/moderate features.

Impotence was determined according to the method described previously[17]. Men were considered candidates for this study when they had complained of erectile dysfunction with diabetic neuropathy for 6 or more months. All candidates had normal results on magnetic resonance image studies of the hypothalamic pituitary axis as obtained by their medical records.

Diabetic treatment was recorded as diet alone, oral hypoglycemic agent or insulin. Inquiry was made of other drug therapy, angina pectoris, previous myocardial infarction or cardiac failure, intermittent claudication, thyroid dysfunction, previous sympathectomy or other abnormality that might predispose to organic impotence such as neurological disease or previous injury.

To assess the efficacy and safety of oral sildenafil citrate (Viagra™-Pfizer) in the treatment of erectile dysfunctions in IDDM/ NIDDM diabetic men with and without neuropathy and in age matched non diabetic controls, subjects home and clinical practice centers in the local vicinities, were randomized to receive sildenafil citrate (50 mg), but not more than once daily, for 12 months. Self-reported ability to achieve and maintain an erection for sexual intercourse according to the International Index of Erectile Function and adverse events were recorded according to the method described

previously[18]

The study design consisted of a prospective cross-over, two period investigation (Pre and Post Ejaculation after the intake of 50 mg Viagra). Erectile and sexual responses were assessed using simultaneous monitoring of Libido, Erection frequency (Angle of erection), Masturbation ability, Ejaculation pattern (Normal/Retrograde) and pattern of Erection lost (Gradual/Abrupt) during laboratory based audiovisual sexual stimulation with film before and after the sildenafil treatment in all the subjects according to the method described previously[17, 19].

The degree of erection to erotic film & fantasy distinguished between neuropathic & non neuropathic etiologies. The initial approach was tentative so that it was easy for the individuals to decline without embarrassment. If there was apparent willingness, a more definite request was made. The time to re-obtain erection after ejaculation (post ejaculatory refractory time) was measured with the stop-watch technique by asking the subject to keep self-stimulating immediately after ejaculation and concomitantly by keeping on watching a different audiovisual sexual stimulation. All the parameters were statistically analyzed using Student *t*-test. In all the instances probability ($p<0.05$) was regarded as statistically significant.

Results

The data for the assessment of libido (%), Erection frequency (Angle of erection), Masturbation ability, Ejaculation pattern (Normal/Retrograde) and pattern of Erection lost (Gradual/Abrupt) before and after the administration of the 50 mgs. of oral dose of sildenafil in 50 IDDM/ NIDDM diabetic men (with and without neuropathy) and in 50 age matched non diabetic control patients is shown in tables-1-5. Sildenafil treatment showed a significant improvement ($P<0.0005$ in some cases) in the pattern of all of the above mentioned parameters during the first ejaculatory phase in both types of diabetic neuropathics and were found to be maintained (absolute) during post-ejaculatory phase as well.

The pattern of libido in sildenafil treated IDDM/ NIDDM patients with neuropathy presented in table-1 was found to be about 100%, with a highly significant difference statistically ($P<0.0005$), when compared before the administration of viagra (almost 0%). This pattern of libido remained the same during the second ejaculation phase as well.

Erection frequency (degree) after the sildenafil treatment presented in (table-2) was found to be about 90^0, and maintained at the same level in the post ejaculatory phase from an untreated value of 45^0 with a highly significant difference statistically ($P<0.0005$).

Sildenafil treatment showed an *absolute* (90%) masturbation ability during the pre and post ejaculatory phases in IDDM/ NIDDM patients with neuropathy (table-3, $P<0.0005$), when compared with untrated subjects i.e. *impaired* (45%).

The pattern of ejaculation (table-4) in IDDM/ NIDDM neuropathics in both the pre and post-ejaculatory samples after the oral administration of 50 mgs. of sildenafil were found to be *normal* when compared before the administration of sildenafil citrate i.e. *retrograde* (Significant differerence).

Similarly the pattern of erection lost in the IDDM/ NIDDM patients with neuropathy in both the pre and post-ejaculatory samples after the oral administration of 50 mgs. of sildenafil citrate was found to be *gradual* when compared with the pattern obtained before the administration of sildenafil i.e. *gradual* (Significant differerence).

However, the difference in the pattern of all the above mentioned sexual parameters was found to be non significant in both types of diabetic patients without neuropathy and when compared with their respective control subjects during the first ejaculatory phase. A complete failure in the pattern of all the erotic responses in these subjects during the post ejaculatory phase was also observed since no erection/ejaculation could be achieved during this phase.

Discussion

The etiology of erectile impotence associated with diabetes mellitus has been reported to be neuropathic abnormality in the male genital organ and/or vascular change in the corpora cavernosa[9]. However assessment of the neuropathic factor has been impended by the lack of an objective laboratory test.

There have been previous reports in the literature that the prevalence of impotence in diabetic men is related to the presence of autonomic neuropathy [6, 8].

Current evidence indicates that erection may involve the activation of several separate mechanisms[20]. In addition to parasympathatically mediated arterial vasodilatation, there may also be active reduction of venous drainage and the active closure of intra cavernosal arterio-venous shunts[21]. None of the established methods of

Table 1. Changes in post-ejaculatory pattern of libido before and after oral administration of Sildenafil citrate (Viagra, 50mg dose) in insulin dependent (IDDM)/ non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls.

Subjects	Post-Ejaculatory Libido Before Viagra Administration		Post-Ejaculatory Libido After Viagra Administration	
	1st Ejaculation	2nd Ejaculation	1st Ejaculation	2nd Ejaculation
Iddm/Niddm Without Neuropathy N=50	Diminished (92%)	No Ejaculation	Complete (100%)	No Ejaculation
Iddm/Niddm With Neuropathy N=50	Absent* (0%)	No Ejaculation	Complete (100%)	Complete (100%)
Non-Diabetic Controls N=50	Complete (100%)	No Ejaculation	Complete (100%)	No Ejaculation

N-represents the total number of subjects examined.
IDDM/NIDDM (with and without neuropathy; 1st and 2nd ejaculation) values are compared before and after the oral administration of Viagra for t-test.
* = P< 0.0005

Table 2. Changes in post-ejaculatory pattern of erection frequency (degree) before and after oral administration of Sildenafil citrate (Viagra, 50mg dose) in insulin dependent (IDDM)/ non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls.

Subjects	Post-ejaculatory Erection frequency Before viagra administration		Post-ejaculatory Erection frequency After viagra administration	
	1st Ejaculation	2nd ejaculation	1st Ejaculation	2nd. ejaculation
Iddm/niddm without neuropathy N=50	Partial Failure of erection (88^0)	No ejaculation	Complete erection (90^0)	No ejaculation
Iddm/niddm with neuropathy N=50	Complete failure of erection* (45^0)	No ejaculation	Complete erection* (90^0)	Complete erection (900)
Non-diabetic controls N=50	Complete erection (90^0)	No ejaculation	Complete erection (90^0)	No ejaculation

N-represents the total number of subjects examined.
IDDM/NIDDM (with and without neuropathy; 1st and 2nd ejaculation) values are compared before and after the oral administration of Viagra for t-test.
* = P< 0.0005

Table 3. Changes in post-ejaculatory pattern of masturbation ability before and after oral administration of Sildenafil citrate (Viagra, 50mg dose) in insulin dependent (IDDM)/ non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls.

Subjects	Post-ejaculatory Masturbation ability Before viagra administration		Post-ejaculatory Masturbation ability After viagra administration	
	1st Ejaculation	2nd ejaculation	1st Ejaculation	2nd ejaculation
Iddm/niddm without neuropathy N=50	Partially Absolute (90%)	No ejaculation	Completely absolute (95%)	No ejaculation
Iddm/niddm with neuropathy N=50	Completely impaired* (45%)	No ejaculation	Completely* absolute (90%)	Completely absolute (90%)
Non-diabetic controls N=50	Completely absolute (95%)	No ejaculation	Completely absolute (95%)	No ejaculation

N-represents the total number of subjects examined.
IDDM/NIDDM (with and without neuropathy; 1st and 2nd ejaculation) values are compared before and after the oral administration of Viagra for t-test.
* = P< 0.0005

Table 4.Changes in post-ejaculatory-ejaculation pattern before and after oral administration of Sildenafil citrate (Viagra, 50mg dose) in insulin dependent (IDDM)/ non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls.

Subjects	Post-ejaculatory Ejaculation pattern Before viagra administration		Post-ejaculatory Ejaculation pattern After viagra administration	
	1st Ejaculation	2nd ejaculation	1st Ejaculation	2nd ejaculation
Iddm/niddm without neuropathy N=50	Almost Normal	No ejaculation	Completely normal	No ejaculation
Iddm/niddm with neuropathy N=50	Retrograde*	No ejaculation	Completely* normal	Completely normal
Non-diabetic controls N=50	Completely normal	No ejaculation	Completely normal	No ejaculation

N-represents the total number of subjects examined.
IDDM/NIDDM (with and without neuropathy; 1st and 2nd ejaculation) values are compared before and after the oral administration of Viagra for t-test.
* = Significantly different

Table 5. Changes in post-ejaculatory pattern of erection lost before and after oral administration of Sildenafil citrate (Viagra, 50mg dose) in insulin dependent (IDDM/ non-insulin dependent (NIDDM) diabetic males (with and without neuropathy) and in age matched non-diabetic controls.

Subjects	Post-ejaculatory Erection loss pattern Before viagra administration		Post-ejaculatory Erection loss pattern After viagra administration	
	1st ejaculation	2nd ejaculation	1st Ejaculation	2nd ejaculation
Iddm/niddm without neuropathy N=50	Gradual	No ejaculation	Gradual	No ejaculation
Iddm/niddm with neuropathy N=50	Abrupt*	No ejaculation	Gradual*	Gradual
Non-diabetic controls N=50	Gradual	No ejaculation	Gradual	No ejaculation

N-represents the total number of subjects examined.
IDDM/NIDDM (with and without neuropathy; 1st and 2nd ejaculation) values are compared before and after the oral administration of Viagra for t-test.
* = Significantly different

investigating penile dysfunction is wholly satisfactory.

Penile rigidity is the most important determinant of the quality of an erection. Based on published evidence it is suggested that a penile rigidity of >70% is adequate for sexual intercourse[22]. Because sildenafil is believed to exert its beneficial effects by inhibiting the phosphodiesterase type-V enzyme and, therefore, increasing the intracellular levels of cGMP in the corporal smooth muscle, it would not be expected to produce an erectile response when used in the absence of a drive on the nitric oxide-cGMP pathway. This drive can be provided by physiological mechanisms that can be initiated by visual or other forms of sexual stimulations. As such, sildenafil may be expected to enhance relaxation of the corpus cavernosal smooth muscle, which in turn increases blood flow into the cavernosal spaces, thus leading to increased intracavernosal pressure, a key factor in producing an erect penis[23].

More recently sildenafil has been reported to be used for the treatment of temporary erectile dysfunctions with assisted reproductive technologies showing a marked reduction of post ejaculatory refractory time. These results indicate that sildenafil treatment has a positive influence over the resumption of erections following ejaculation in the presence of a continuous erotic stimulus and has the potential to facilitate multiple instances of sexual intercourse in the presence of a continuous erotic stimulation[24, 25].

This study has been therefore further designed to determine if sildenafil citrate administered orally in single doses effectively improved penile erections and restores post-ejaculatory erectile and sexual responses in both IDDM/ NIDDM diabetics with erectile dysfunctions for which there was an established neuropathic cause, and to evaluate the efficacy and safety of sildenafil citrate in such patients.

Our results indicated that the pattern of libido, erection frequency, masturbation ability, pattern of ejaculation and the pattern of erection lost as a result of psycho-sexual stimulation in IDDM/ NIDDM patients with neuropathy after the oral administration of 50 mgs. of sildenafil citrate were found to be *absolute* (100% functional), when compared before the administration of Sildenafil citrate i.e. *impaired* (failure), and were found to be maintained (absolute) during post-ejaculatory phase as well.

However this difference was found to be non-significant in both types of diabetic patients without neuropathy after oral administration of sildenafil citrate and when compared with their respective control subjects.

These observations are consistant with the presence of both a domaminergic and a serotonergic control system, which normally exert a positive and inhibitory influence over the resumption of mating following ejaculation respectively. Since dopamine and serottonin do

not utilize cGMP as a second messenger[26,27], it is unlikely that sildenafil-induced reduction of the post ejaculatory refractory time is due to an interaction with central monoaminergic control pathways.

On the other hand, sildenafil-induced reduction of the post ejaculatory interval may be explained by its relatively long plasma half life (about 4 hours) and a consequant prolonged inhibition of intracavernosal PDE5[28,29].

Our results are in consistency with the above mentioned findings and proves that sildenafil citrate is an effective fist-line therapy for erectile dysfunction in diabetic men with impotence of neuropathic etiology. These results further explains, how to manage sexual disorders as part of diabetic care, and suggests rules for viagra's prescription in diabetic neuropathic patients and may prevent both stress and frustration for these couples in case a first intercourse is not successful.

In conclusion, even if further studies are needed to evaluate the effects of chronic sildenafil treatment on fertility capacity, our results indicate that sildenafil has the ability to reduce the post ejaculatory refractory time in the presence of a continuous psycho-sexual stimulus adds a new aspect of interest in the research area concerning the regulatory mechanisms of male copulatory behaviour.

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