Cardiovascular Effects of Sildenafil in Men with SCIs at and Above T6

Marcalee Sipski, Craig Alexander, Xiahuo Guo, Angelo Gousse, and Raymond Zlamal

Purpose: To determine the cardiovascular effects of sildenafil in men with spinal cord injuries (SCIs) at and above the level of T6, we conducted a double-masked, placebo-controlled laboratory-based study. Method: Participants received sildenafil 50 mg or lactose placebo on alternating days 1 hour prior to a 78-minute experimental protocol. Six-minute baseline periods alternated with two 12-minute audiovisual stimulation periods. Participants include 10 men with traumatic SCIs, mean age of 43. Results: Results revealed significant increases in penile circumference with sildenafil compared to placebo ($p = .0035$). Although there was a trend for patients to acknowledge higher levels of arousal while on sildenafil, results were not statistically significant. Moreover, although there was a trend toward decreased blood pressure and increased heart rate with the use of sildenafil, differences were not statistically significant. Conclusion: Based upon these findings, sildenafil appears to be a safe, effective drug to use in men with SCIs at and above T6.
Key words: *erectile dysfunction, SCI, sildenafil*

Sildenafil is the only Food and Drug Administration (FDA)-approved oral agent that is effective for remediation of erectile dysfunction.[1] Moreover, it has been shown to be effective in men with spinal cord injuries (SCIs) and is known to be a first-line agent for treating erectile dysfunction in this population.[2] One study showed that 75% of 12 men with SCIs on sildenafil as compared to 7% of 14 patients on placebo reported the treatment had improved their erections after 28 days of therapy.[3] Another report of 178 patients with SCI enrolled in a double-blind, randomized, placebo-controlled, two-way flexible dose crossover study indicated that 76% of men found that sildenafil im-

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proved their ability to have erections, and they preferred sildenafil as compared to placebo. For all men, 80% reported that sildenafil improved sexual intercourse as compared to only 10% who noted improvement with placebo. Adverse events necessitated discontinuation of drug in 2% of treatment patients as compared to 1% of placebo, and no significant adverse events were noted with sildenafil.[4] Yet another report assessed the responses of 17 men with SCI who used sildenafil on an at-home basis, noting the drug is effective and well tolerated in men with erectile dysfunction related to SCI.[5]

Despite the overall positive results with sildenafil in men with SCIs, there have been concerns raised about the use of drug in men with SCIs at T6 and above. These concerns have been related to the potential that men with injuries at T6 and above have for dysreflexia during sexual activity and the potential for the use of nitroglycerin to treat their dysreflexia. However, we recently performed a laboratory-based study of the effects of sildenafil in women with SCIs during sexual arousal and noted that sildenafil had a mild hypotensive effect, thus it may actually be protective against dysreflexia.[6] Moreover, we have observed through another laboratory-based study of 68 women with SCIs that none of the women became dysreflexic during sexual stimulation.[7] Thus, we believe, the assumption that men with SCIs at and above T6 would become dysreflexic and subsequently use nitroglycerin while using sildenafil is particularly unfounded. In contrast, we believe the use of sildenafil in men with SCIs at and above T6 is safe. Moreover, we hypothesize that the impact of sildenafil on cardiovascular responses during sexual stimulation should be similar to that in women: producing mild hypotension and a mild increase in heart rate as compared to placebo. The present study was undertaken to evaluate the cardiovascular and genital effects of sildenafil in men with SCIs at T6 and above.

Method

All study procedures were approved by the Human Subjects Committee at our institution. Participants were recruited from the population of inpatient and outpatient veterans who were treated at the Miami VA Medical Center. Upon expressing interest in the study, participants were provided with and signed an informed consent. Participants were then evaluated for study participation. Study procedures took place at the sexual physiology laboratory on the SCI unit at the Miami VA Medical Center. Participants underwent a medical history and physical in addition to being classified according to the *International Standards for Neurological and Functional Classification of Spinal Cord Injury*, revised 2000.[8]

Participants

Participants for this study included 10 men with traumatic SCIs with a mean age of 43 years (range, 23–55). Age at injury ranged from 20 to 47 with a mean age at injury of 30. Characteristics of individual participant's neurologic injuries are described in **Table 1**. Six participants had complete injuries while four were incomplete. Mean injury level was C7. For study participation, participants had to be free from active medical or psychiatric dysfunction and have had an EKG within the past year.

The study design was a double-masked, placebo-controlled, crossover design. Sildenafil 50-mg tablets and lactose placebos

Table 1. Neurologic characteristics of participants ($N = 10$)

Characteristic	1	2	3	4	5	6	7	8	9	10
Level of injury	7	6	6	5	5	7	4	12	5	13
Total motor score	30	9	19	46	67	39	60	76	2	50
T11-L2 pinprick score	0	0	0	0	16	7	8	8	0	0
S3-5 pinprick score	0	0	0	0	8	0	4	1	0	0
T11-L2 light touch score	0	0	0	12	16	7	6	8	0	0
S3-5 light touch score	0	0	0	0	8	3	1	3	0	0
Voluntary rectal contraction	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Injury type affecting S3-S5	UMN	UMN	UMN	UMN	UMN	UMN	UMN	UMN	UMN	UMN
Bladder control	A	A	A	A	A	A	I	A	A	A
Bowel control	A	A	A	A	A	A	P	A	A	A

Note: UMN = upper motor neuron; A = absent; I = intact; P = partial.

of identical weight and appearance were prepared by the hospital pharmacy and were provided to the investigators. Once informed consent had been obtained and the physical examination performed, participants' baseline blood pressure and cardiovascular parameters were obtained; when participants were stabilized, they received either placebo or 50 mg of sildenafil. Blood pressure readings were performed with the participants seated in bed.

Blood pressure (BP) and heart rate (HR) readings were then taken every 3 minutes. One hour after drug administration, participants began the experimental protocol. This consisted of a 78-minute protocol with four 12-minute periods of erotic stimulation interspersed with 6-minute baseline periods, similar to that used in previous studies of female sexual response.[7] During periods 1 and 2, participants viewed an erotic video without performing any genital stimulation; during periods 3 and 4, participants viewed an erotic video in conjunction with performance of self-applied manual penile stimulation. (Because participants were wearing the Rigiscan during this time, they were instructed not to touch the rings during stimulation.) BP and HR readings were performed every 3 minutes throughout the study protocol, as were penile circumference and rigidity measurements. For these measurements, readings at the tip and base were monitored with the Rigiscan. Participants were also asked to verbally provide their subjective level of arousal (SA) in a fashion similar to previous research[7] ("How emotionally aroused are you on a scale of 1–10?") every 3 minutes. After study completion, participants were asked to stay until their BP and HR readings returned to baseline.

At the next study session, participants were initially queried as to whether they had any side effects the previous day or evening. Then, the identical procedure was followed with the exception that participants received the alternate drug: sildenafil or lactose placebo. After study completion on day 2 as on day 1, participants were asked to remain until their BP and HR readings returned to baseline.

Data analysis

Data analysis consisted of a two-factor, within-subjects, repeated-measures design. Means and standard deviations were calculated for each of the primary response variables, including combined base and tip measurements for penile circumference and rigidity, SA, HR, and systolic and diastolic blood pressures (SBP, DBP). Analysis of variance (ANOVA) was performed using a mixed model analysis (SPSS Version 10.0; SPSS, Inc., Chicago, IL) to examine main effects and interactions for drug and stimulation conditions. We used one-tailed tests of significance for drug effects, with the hypothesis that sildenafil would increase HR and decrease BP within safe levels. In addition, we expected that penile circumference and SA would increase.

Results

Penile circumference and rigidity

The effects of drug and stimulation condition on penile circumference and rigidity are shown in **Table 2**; the effects on rigidity are displayed in **Figure 1**. ANOVA revealed significant increments in penile circumference ($p = .0035$) with the use of sildenafil compared with placebo. A borderline signifi-

Table 2. Sexual function effects of sildenafil in men (mean ± *SD*)

Drug	Visual stimulation (mean ± *SD*)	Visual + manual stimulation (mean ± *SD*)	*F*	*p*
Penile circumference				
Sildenafil	17.15 ± 2.74	18.31 ± 3.39	16.77	.0035
Placebo	15.36 ± 2.52	16.28 ± 2.50		
Rigidity				
Sildenafil	2.73 ± 3.59	13.07 ± 18.31	0.73	.4187
Placebo	0.28 ± 0.85	7.69 ± 15.66		
Subjective arousal				
Sildenafil	3.42 ± 1.53	4.76 ± 1.86	1.61	.2396
Placebo	3.42 ± 1.40	3.82 ± 2.90		

cant effect of sexual stimulation was observed ($p = .0710$), with increasing level of penile circumference from visual to visual plus manual stimulation. ANOVA also revealed significant changes in rigidity ($p = .0437$) with increasing levels of sexual stimulation. The drug effect was not significant, but the mean difference was in favor of sildenafil over placebo in both sexual stimulation conditions.

Subjective arousal

As shown in **Table 2**, neither drug administration ($p = .2396$) nor stimulation ($p = .2290$) brought significant changes in sub-

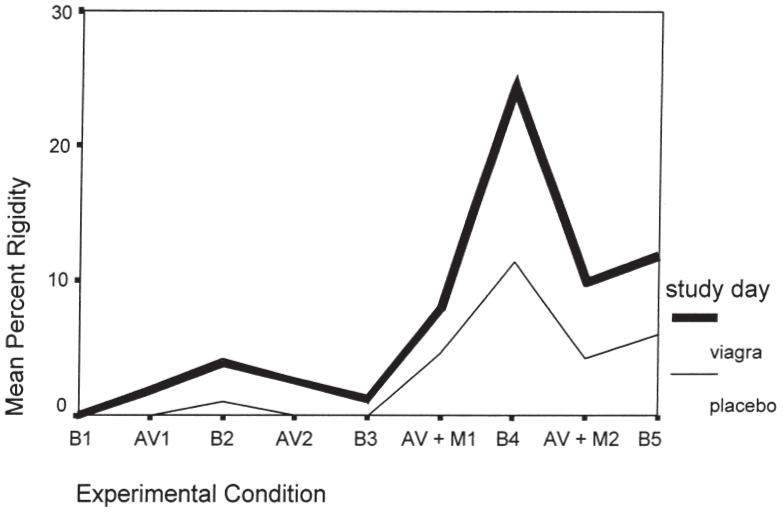

Figure 1. Penile rigidity during various conditions. B = baseline; AV = audiovisual; M = manual.

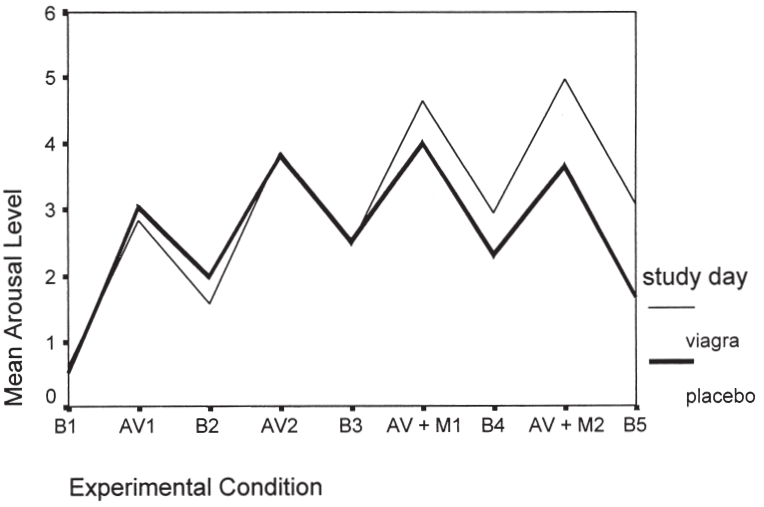

Figure 2. Arousal levels during various conditions. B = baseline; AV = audiovisual; M = manual.

jective arousal level. There was a trend (see **Fig. 2**), however, for patients to acknowledge higher levels of arousal while on sildenafil.

Heart rate and blood pressure

Table 3 presents effects of drug and stimulation on HR. ANOVA demonstrated no significant changes associated with sildenafil. But the effect of stimulation was borderline significant ($p = .0603$); there was higher HR with visual plus manual stimulation than during visual stimulation alone.

Drug and stimulation effects on DBP and SBP are also shown in **Table 3**. The results are similar to HR, with no significant effects of sildenafil on either DBP or SBP. ANOVA

Table 3. Cardiovascular function effects of sildenafil in men

Drug	Baseline (mean + *SD*)	Visual stimulation (mean + *SD*)	Visual + manual stimulation (mean ± *SD*)	*F*	*p*
DBP (mm Hg)					
Sildenafil	67.7 ± 12.0	66.9 ± 11.6	70.3 ± 10.2	1.81	.2159
Placebo	71.4 ± 8.6	70.3 ± 9.9	75.8 ± 7.7		
SBP (mm Hg)					
Sildenafil	120.1 ± 14.5	118.4 ± 15.0	129.5 ± 20.8	.48	.5079
Placebo	124.8 ± 11.1	120.4 ± 11.6	134.4 ± 14.6		
HR (bpm)					
Sildenafil	65.3 ± 11.9	63.4 ± 13.4	66.9 ± 13.6	.94	.3607
Placebo	62.6 ± 8.2	61.7 ± 7.9	64.4 ± 9.5		

Note: DBP = diastolic blood pressure; SBP = systolic blood pressure; HR = heart rate; bpm = beats per minute.

showed that the effect of stimulation on SBP was significant ($p = .0243$) and on DBP was borderline significant ($p = .0811$). Both blood pressures were higher during audiovisual plus manual stimulation than during audiovisual stimulation alone.

Discussion

Results of this pilot study, though they do not reach statistical significance, reveal a trend in patients with SCIs at the level of T6 and above toward the development of decreased BP and increased HR with the use of sildenafil 50 mg as compared to placebo. These results are consistent with findings in able-bodied men where single oral doses of sildenafil 200 mg produced mean maximal decreases in supine blood pressure of 8.5/5.5 mm Hg approximately 1–2 hours after dosing[9] and are similar to findings during exercise in men with known or probable coronary artery disease.[10] Because sildenafil produces a hypotensive effect during sexual activity, it may actually provide a somewhat protective effect against autonomic dysreflexia in patients with SCIs at the level of T6. Nevertheless, should dysreflexia occur, the use of nifedipine is not contraindicated and patients could safely be treated through this route.

Results of this study also demonstrated a significant increase in penile circumference through use of the drug, accompanied by a trend to increased rigidity and increased level of subjective arousal. These findings are consistent with the known efficacy in patients with SCIs. In general, SCI patients with injuries at and above T6 should respond to sildenafil; however, the required dose is variable. Previous reports have shown that 58% of 41 participants with SCIs who were treated with sildenafil demonstrated functional erections 1 hour after 50 mg of sildenafil, whereas 37% of participants required doses of 75–100 mg.[11]

Sexual function is an important aspect of life for men with SCIs, and feelings related to the ability to have sexual intercourse are an important determinant of sexual satisfaction for many men with SCIs.[12] Although many means to remediate erectile dysfunction exist, all of them are fraught with potential complications and some may result in aesthetically unpleasant erections.

The use of the vacuum constriction device is often suggested as a noninvasive means to improve erectile capability. However, the use of the device can produce complications. Use of vacuum constriction is contraindicated in individuals who are on anticoagulation medication or who have blood dyscrasias. Related known complications include ecchymoses, petechiae, and gangrene in an individual who failed to remove the device after the recommended 30-minute maximum.[13] Vacuum constriction devices are also difficult to apply and take time out of a sexual encounter. Because they produce an erection through engorgement of both corporeal and noncorporeal tissues, the erection may have a greater circumference than the person's baseline and the skin may be discolored. Pivoting may also occur at the base of the penis during the time of the erection, which can interfere with penile control during intercourse and result in repeated dislocation of the penis from the vagina.[14] Another complaint is coolness of the penis, which decreases the partner's ability to enjoy satisfactory intercourse.[15] For all of these reasons, many individuals with SCIs prefer not to use vacuum suction devices to improve their ability to achieve erection.

Another means to remediate erectile dys-

function is through the use of prostaglandin E_1 or alprostadil, which is available via intracavernosal injection and via intraurethral application. Unfortunately, both methods of administration require a physical intervention to produce an erection and this can be a source of interruption to the flow of sexual activity. In addition, both means of administration share the potential risks of priapism, therefore patients who are prone to venous thrombosis or hyperviscosity syndromes need to be treated with caution. The intraurethral form of administration can also result in hypotension. The use of injection therapy can lead to potential bleeding complications, so patients on anticoagulants need to be treated with caution. Moreover, penile fibrosis has been reported as a complication in up to 7.8% of patients, and priapism was noted in up to 4% of patients who used intracavernosal injections for up to 18 months.[16] With regard to efficacy, the quality of erections reported with intracavernosal alprostadil is often considered superior to those obtained with vacuum devices, and patients may be willing to tolerate the associated risks with use of the drug. However, documented efficacy of intraurethral alprostadil is marginal.

All of the alternatives to treat erectile dysfunction have potential side effects. Sildenafil, currently the only FDA-approved oral medication, also has potential side effects; the most significant drawback is the need to avoid concomitant use of nitroglycerin that can result in life-threatening hypotension. Other side effects include headaches (16%), flushing (10%), dyspepsia (7%), and transient visual disturbances that predominantly consist of color tinge to vision but also can include increased sensitivity to light or blurred vision (3%).[17] Priapism is also a known complication. Although its incidence is infrequent, patients with a history of priapism or predisposition should avoid the use of sildenafil. In general, however, after comparison of the complications related to all of the treatments, sildenafil is an easy to use and relatively effective alternative for the promotion of erectile responses in men with SCIs.

As demonstrated by Schmid et al.,[11] sildenafil is not universally efficacious in patients with SCIs despite its documented safety, convenience, and efficacy. Those participants who have complete absence of reflexive and psychogenic erections appear to be nonresponders to the drug, probably because an absence of neural innervation to the penis. In these participants, combined use of vacuum constriction devices[18] or the use of intraurethral alprostadil[19] should be considered as a means to promote the development of erections. Moreover, as other new treatments are developed and are FDA-approved for erectile dysfunction, rapid consideration should be given to document their safety and efficacy profiles in individuals with SCIs.

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REFERENCES

1. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med.* 1998;338:1397–1404.
2. Green BG, Martin S. Clinical assessment of sildenafil in the treatment of neurogenic male sexual dysfunction: after the hype. *Neuro-Rehabilitation.* 2000;15:101–105.
3. Derry FA, Dinsmore WW, Fraser M. Efficacy and safety of oral sildenafil (Viagra) in men with erectile dysfunction caused by spinal cord injury. *Neurology.* 1998;51:1629–1633.
4. Giuliano F, Hultling C, El Masry WS, Smith MD, Osterloh IH, Orr M, Maytom M. Randomized trial of sildenafil for the treatment of erectile dysfunction in spinal cord injury. *Ann Neurol.* 1999;46:15–21.
5. Gans WH, Zaslau S, Wheeler S, Galea G, Vapnek JM. Efficacy and safety of oral sildenafil in men with erectile dysfunction and spinal cord injury. *J Spinal Cord Med.* 2001;24:35–40.
6. Sipski ML, Rosen RC, Alexander CJ, Hamer RM. Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology.* 2000;55:812–815.
7. Sipski ML, Alexander CJ, Rosen R. Sexual arousal and orgasm in women: effects of spinal cord injury. *Ann Neurol.* 2001;49:35–44.
8. *International Standards for Neurological and Functional Classification of Spinal Cord Injury*, revised 2000. Chicago, IL: American Spinal Injury Association.
9. Information on Viagra. *Physicians' Desk Reference.* 54th edition. Montvale, NJ: Medical Economics; 2000: 2382.
10. Arruda-Olsen AM, Mahoney DW, Nehra A, Leckel M, Pellikka PA. Cardiovascular effects of sildenafil during exercise in men with known or probably coronary artery disease. *JAMA.* 2002;287:719–725.
11. Schmid DM, Schurch B, Hauri D. Sildenafil in the treatment of sexual dysfunction in spinal cord-injured male patients. *Eur Urol.* 2000;38:184–193.
12. Alexander CJ, Sipski ML, Findley TW. Sexual activities, desire, and satisfaction in males pre- and post-spinal cord injury. *Arch Sex Behav.* 1993;22(3):217–228.
13. Rivas DA, Chancellor MB. Complications associated with the use of vacuum constriction devices. *J Am Paraplegia Soc.* 1994;17:137–140.
14. Rivas DA. Management of erectile dysfunction. In: Sipski ML, Alexander CJ, eds. *Sexual Function in Disability and Chronic Illness: A Health Practitioners Guide.* Gaithersburg, MD: Aspen Publishers; 1997:452.
15. Turner LA, Althof SE, Levine SB, et al. Treating erectile dysfunction with external vacuum devices: impact upon sexual, psychological and marital functioning. *J Urol.* 1990;144:79–82.
16. Information on Caverject. *Physicians' Desk Reference.* 54th edition. Montvale, NJ: Medical Economics; 2000:2419.
17. Information on Viagra. *Physicians' Desk Reference.* 54th edition. Montvale, NJ: Medical Economics; 2000:2384.
18. Raina R, Agarwal A, Lakin MM, Zippe C. Combination therapy: sildenafil citrate enhances sexual satisfaction in vacuum constriction device (VCD) failures following radical prostatectomy (RRP). Abstract presented at meeting of AUA; Orlando, Florida; May 2002.
19. Jaffe JS, Antell M, Ginsberg PC, Price A, Harkaway R, Greenstein M. Use of Intraurethral alprostadil (Muse) in a group of Sildenafil citrate non-responders. Abstract presented at meeting of AUA; Orlando, Florida; May 2002.