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Original Article

Determination of changes in blood pressure during administration of sildenafil (Viagra®) in patients with spinal cord injury and erectile dysfunction

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Study design: Prospective, open-label, comparative study, to assess the effects of sildenafil on blood pressure in a population of patients with spinal cord injury (SCI).

Objectives: To determine the effect of sildenafil on blood pressure in patients with erectile dysfunction secondary to SCI by comparing changes in blood pressure in SCI patients with a neurologic level below T5 *versus* higher levels. To establish a relationship between the potential hypotensive effect and protective muscle spasm against blood pressure reduction. To assess the effects of age, complexity and duration of SCI on changes in blood pressure. To record any adverse effects occurring during the study.

Setting: Spinal Cord Injury Unit, Insular University Hospital of Gran Canaria, Canary Islands, Spain.

Subjects: In total, 22 male SCI patients aged 18 years or older with a history of SCI greater than 3 months in duration.

Methods: Patients with erectile dysfunction secondary to SCI were induded in the study, without excluding patients with a neurologic level above 75 or asymptomatic low blood pressure. Patients with specific contraindications for use of the drug were excluded. A personal history was obtained, and the level of injury (ASIA/IMSOP scales of international standards), impairment grade (ASIA impairment scale), spasticity grade (modified Ashworth scale) and baseline sitting and supine blood pressure values were determined. A single dose of 50 mg of sildenafil was administered, and patients remained sitting at 45°. Blood pressure was monitored every 10 min for 4 h and whenever the patient reported symptoms. Any relevant signs and symptoms manifested during the study period were also recorded. Analysis of the changes in blood pressure values was performed using a paired t-test in each group of patients according to neurologic level and spasticity grade.

Results: A decrease in blood pressure was observed in all patients, although patients with a level of injury at T5 or above and those with a complete SCI showed a less intense decrease ($P < 0.05$). The spasticity grade of the patients was protective against the fall in blood pressure, as it was less significant in patients with grade 3 ($P > 0.1$) than in those with grade 0. Adverse effects were few and transient. None were related to hypotension.

Conclusion: Sildenafil caused a decrease in blood pressure in SCI patients with a neurologic level of injury above T5 and complete injuries (grade A), but did not have clinical implications in the patients studied. A higher spasticity grade tends to protect the patient from the fall in blood pressure. Age and duration of injury do not appear to influence this decrease.

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Keywords: spinal cord injury; erectile dysfunction; sildenafil; hypotension; blood pressure

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Introduction

Erectile dysfunction (ED), defined as the consistent inability to attain and/or maintain an erection sufficient for satisfactory sexual intercourse,[1] is a common

complication in men with spinal cord injuries (SCI). In total, 80% of these patients have some type of erection, either reflex, psychogenic or mixed.[2] However, most of these erections are inadequate to engage in satisfactory sexual contacts and usually require some type of therapeutic intervention.

In recent years, the incorporation of sildenafil citrate (Viagra[R]) into the therapeutic arsenal for ED has opened a door of hope for treatment of this sexual disorder in individuals with SCI. It has been used and its efficacy and good tolerance have been demonstrated in patients affected by ED of nearly all etiologies,[3–5] including patients with SCI.[6–8]

Relaxation of smooth muscle in the corpus cavernosum is a prerequisite for normal erectile function.[9] Nitric oxide plays a key role as a mediator of smooth muscle relaxation in the corpus cavernosum and penile erection in response to sexual stimulation through a mechanism of induction of cyclic guanosine monophosphate (cGMP).[9,10] Sildenafil is an orally active selective inhibitor of cGMP-specific phosphodiesterase 5, which metabolizes cGMP in the corpus cavernosum in humans.[11] By inhibiting hydrolysis of cGMP in the corpora cavernosa, sildenafil restores the natural erectile response to sexual stimuli in patients with ED.

A number of studies have been conducted that demonstrate the efficacy of sildenafil.[2,6–8,13–16] In all these studies, sildenafil was reported to have notable efficacy for obtaining and maintaining an erection in patients with SCI. However, in many of these studies,[2,6,7] patients with neurological levels of SCI above T5 were systematically excluded due to the potential risk of autonomic dysreflexia and, especially, of hypotension. Similarly, many of the studies excluded individuals with hypotension (systolic/diastolic blood pressure <90/50 mmHg, respectively).[2,6,7,15]

The hypotensive tendency of patients with SCI is widely known, which is more intense the higher the neurologic level affected and the greater the persisting muscular flaccidity.[17,18] This circumstance imposes certain restrictions on the use of sildenafil in SCI patients with cervical and high thoracic neurologic levels. Hence, the repeated exclusion of these patients in the previously mentioned studies.

However, on performing a detailed review of all the studies on the safety of sildenafil for the treatment of ED in SCI patients, we found that only in the study by Gans et al[13] was a case of hypotension related to this treatment reported. It was this study, which did not exclude SCI patients with high neurologic levels, although it does not specify the underlying blood pressure alterations.

It is not illogical to think that a phosphodiesterase inhibitor could have a hypotensive effect. Although sildenafil is specific in its action on phosphodiesterase 5, which is primarily distributed in the corpora cavernosa of the penis, it is also found in smaller amounts in platelets, skeletal muscle, visceral and vascular smooth muscle.[19,20] In fact, it has been found that sildenafil causes vasodilatation with a decrease of 10 mmHg for systolic blood pressure and 7 mmHg for diastolic blood pressure in healthy patients.[12] However, our experience with the treatment of ED in patients with SCI has led us to have certain doubts about the level of exclusion for use of sildenafil, since hypotensive symptoms have not been reported by any of our patients.

Objectives

The objectives proposed in this study were (a) to determine in an objective and controlled manner the effect that administration of sildenafil (Viagra[R]) for the treatment of ED has on blood pressure in patients with SCI; (b) to compare the changes in blood pressure levels of patients with a neurologic level of SCI below T5 with those with a neurologic level at T5 or above; (c) to attempt to establish a relationship between the potential hypotensive effect and the protective muscle spasm against the fall in blood pressure; (d) to assess the influence of the complexity of SCI, patient age at the time of the test and duration of injury on blood pressure changes; and, finally (e), to record any adverse effects occurring during the administration of sildenafil (Viagra[R]).

Methods

All male patients aged 18 years or older with ED secondary to SCI and a duration of injury greater than 3 months treated during the acute phase in our SCI Unit were included in the study. Patients with genital anatomic deformities responsible for ED or with known or suspected vascular or endocrine causes of ED, patients with significant documented hematological, renal or hepatic disorders, diabetes mellitus, a history of coagulation disorder or active peptic ulcer were excluded. Subjects with severe cardiovascular dysfunction such as unstable angina or severe heart failure uncontrolled with medications, patients with a recent history (<3 months) of stroke or acute myocardial infarction and patients receiving nitrates or anticoagulants, as well as those who had a history of excessive alcohol intake and risk of repeated intake in excess of 28 units of alcohol/week were also excluded.

All patients included in the study were informed and provided written information about the purpose of the test. After giving consent for their participation, a general history and data on the characteristics of their SCI and events related to their previous sexual activity were collected. Patients then had a physical examination which included, among other aspects, muscle tone (assessed by the modified Ashworth scale).[21] Assessment of their neurologic level of injury (according to the ASIA/IMSOP scales of international standards) and impairment grade (according to the ASIA impairment scale) was also carried out. Immediately before administration of sildenafil (Viagra[R]), sitting and supine blood pressure values were measured.

After completing the baseline study, a single dose of 50 mg of sildenafil (Viagra[R]) was administered, and

blood pressure was monitored automatically (General Electrics Marquette Dash 3000 Monitor) every 10 min during the following 4 h and at any other time if the patient reported symptoms related to hypotension. Patients remained in bed, but sitting at 45°. During the control period, all symptomatic events and signs manifested by patients were recorded.

In the event that a patient developed symptomatic hypotension, it was the protocol existing in this unit for this clinical situation that was applied, based on postural control (Trendelemburg position) and pharmacologic treatment if there was no response (etilefrine hydrochloride).

The study was conducted after prior consultation of the Ethics Committee of the hospital, who gave their approval for the study protocol.

Statistical analysis was performed with SPSS 11.0 using the paired t-test for related samples ($P < 0.05$) in each group of patients according to neurologic level and spasticity grade.

Results

General data on the study population

There were 22 patients who met the criteria for inclusion in the study, with ages between 20 and 47 years and a mean age of 32.86 ± 7.74 years (mean + SD). None of the patients refused to participate in the study. Mean duration of ED (time since SCI) was 6 ± 7.6 years (range 0.33–26.91 years). Of the recruited patients, eight (36.36%) were smokers, 20 (90.91%) were nondrinkers and only two (9.09%) drank alcohol regularly, but always in amounts <28 units of alcohol/week. None of the patients had used any medical treatment for ED.

Recruited patients were divided into two groups based on the neurologic level of injury. In group 1, there were 12 (54.5%) patients with a neurologic injury at T5 or above, and in group 2 there were 10 (45.5%) patients with a neurologic injury below T5. The results of the ASIA classification were as follows: 12 patients were ASIA grade A (54.5%), two were grade B (9.1%), three were grade C (13.6%) and five were grade D (22.7%). The distribution of the general characteristics of the patients in each group is given in Table 1.

Spasticity was assessed by the modified Ashworth scale 35 with the following results: five patients were grade 0 (22.7%), five were grade 1 (22.7%), seven were grade 2 (31.8%) and five were grade 3 (22.7%).

The overall results obtained for baseline blood pressure were as follows mean sitting systolic blood pressure was 124 ± 18.49 mmHg (mean ± SD) and mean supine systolic blood pressure was 126 ± 17.05 mmHg; while mean sitting diastolic blood pressure was 76 ± 12.96 mmHg and mean supine diastolic blood pressure was 76 ± 14.27 mmHg.

An overall analysis of the changes in blood pressure observed in the measurements made over the 4 h of monitoring following administration of 50 mg of sildenafil revealed that the greatest difference between

Table 1 General patient data distributed by study group: group 1, patients with neurologic level of SCI above T5; group 2, patients with neurologic level of SCI below T5

	Group 1	Group 2
N	12 (54.5%)	10 (45.5%)
Levels	C4 (1)	T8 (1)
	C5 (3)	T9 (1)
	C6 (3)	T10 (2)
	C7 (2)	T11 (2)
	T1 (1)	T12 (3)
	T2 (1)	L1 (1)
	T4 (1)	
ASIA		
A	7 (58.3%)	5 (50%)
B	1 (8.3%)	1 (10%)
C	2 (16.6%)	1 (10%)
D	2 (16.6%)	3 (10%)
Muscle tone (modified Ashworth scale)		
0	1 (8.3%)	4 (40%)
1	2 (16.6%)	3 (30%)
2	5 (41.6%)	2 (20%)
3	4 (33.3%)	1 (10%)
Mean blood pressure		
Systolic	125 ± 22.17	123 ± 12.62
Diastolic	74 ± 13.97	78 ± 11.67
Lowest mean blood pressure after administration (mmHg)		
Systolic	99	114
Diastolic	58	64
Maximum mean fall in blood pressure (mmHg)		
Systolic	26	9
Diastolic	16	17
Time between maximum fall in blood pressure and drug administration (min)		
Systolic	120	120
Diastolic	60	30

maximum and minimum mean systolic and diastolic blood pressure was: 17.50 mmHg (maximum mean systolic blood pressure − minimum mean systolic blood pressure) and 11 mmHg (maximum mean diastolic blood pressure − minimum mean diastolic blood pressure tension), respectively, which occurred at 90 min of sildenafil administration.

Level of injury

Analysis of mean blood pressure at baseline in the two patient groups by level of injury found that the group with a neurologic level at T5 or above had a mean systolic blood pressure of 125 ± 22.17 mmHg and a mean diastolic blood pressure of 74 ± 13.97 mmHg, while the patient group with a neurologic level below T5 had a

mean systolic blood pressure of 123 ± 12.62 mmHg and a mean diastolic blood pressure of 78 ± 11.67 mmHg.

The maximum differences observed during the monitoring period in systolic and diastolic blood pressure in patients with a neurologic level at T5 or above (group 1) were 26 and 17 mmHg, respectively, at 120 and 30 min of administration; the maximum differences in systolic and diastolic blood pressure in patients with a neurologic level below T5 (group 2) were 9 and 4.7 mmHg, respectively, both at 120 min. A more detailed analysis of the data obtained for systolic and diastolic blood pressure during monitoring at 30, 60, 120, 180 and 240 min found a significant decrease on all measurements ($P < 0.05$) in group 1. However, in group 2, in spite of the fact that a decrease in blood pressure was also observed on all measurements, the difference did not reach statistical significance (Table 2).

Spasticity grade

With regard to the effect of spasticity on the changes in blood pressure results, we found that mean sitting blood pressure for each spasticity grade was as follows: grade 0, 124 ± 19.14 mmHg in systolic and 77 ± 11.05 mmHg in diastolic blood pressure; grade 1, 139 ± 9.47 mmHg in systolic blood pressure and 83 ± 22.36 mmHg in diastolic blood pressure; grade 2, 112 ± 14.46 in systolic blood pressure and 72 ± 8.84 mmHg in diastolic blood pressure; and grade 3, 127 ± 10.42 and 74 ± 3.26 mmHg in systolic and diastolic blood pressure, respectively. The maximum differences in each group were distributed as follows: grade 0, 10 mmHg in systolic blood pressure at

180 min and 6.40 mmHg in diastolic blood pressure at 120 min; grade 1, 24.80 mmHg in systolic blood pressure at 120 min and 17.6 mmHg in diastolic blood pressure at 60 min; grade 2, 18.29 mmHg in systolic blood pressure at 120 min and 12 mmHg in diastolic blood pressure at 60 min; and grade 3, 11.6 mmHg in systolic blood pressure at 180 min and 4.20 mmHg in diastolic blood pressure at 120 min. These decreases in both systolic and diastolic blood pressure showed some significant values ($P < 0.05$) in patients with spasticity grade 0 on the modified Ashworth scale and to a lesser extent in those with grade 2. Patients with grade 3 had the decreases with least statistical significance with values of $P > 0.1$ on nearly all measurements. In some patients with spasticity grade 3, there was even a slight increase in blood pressure *versus* baseline (Table 3).

Complexity of injury

The changes in blood pressure observed after administration of sildenafil were also evaluated based on the degree of complexity of the SCI (according to the ASIA impairment scale). Patients were divided into two groups: complete injuries (grade A) with 12 patients (54.5%) and incomplete injuries (grades B, C, D) with 10 patients (45.5%). In the complete injury patient group, mean systolic blood pressure was 129 ± 19.10 mmHg and mean diastolic blood pressure was 81 ± 13.73 mmHg; while in the incomplete injury patient group mean systolic blood pressure was 118 ± 16.70 mmHg and mean diastolic blood pressure was 69 ± 8.33 mmHg.

Table 2 Changes recorded in blood pressure after administration of sildenafil (Viagra®) at 30, 60, 120, 180 and 240 min by neurologic level of SCI

Group		BP recording	Mean BP difference $\pm$ SD	Significance level (P<0.05)
1	Systolic BP	BSSBP-SYS30′	14.89 ± 22.25	0.080
		BSSBP-SYS60′	21.33 ± 22.28	0.021
		BSSBP-SYS120′	26 ± 18.24	0.003
		BSSBP-SYS180′	20.89 ± 17.92	0.008
		BSSBP-SYS240′	21.89 ± 24.16	0.026
	Diastolic BP	BSDBP-DIA30′	17.11 ± 17.08	0.006
		BSDBP-DIA60′	16.22 ± 17.14	0.022
		BSDBP-DIA120′	14.78 ± 15.36	0.020
		BSDBP-DIA180′	16 ± 11.4	0.003
		BSDBP-DIA240′	16 ± 14.76	0.012
2	Systolic BP	BSSBP-SYS30′	2.08 ± 10.45	0.487
		BSSBP-SYS60′	2.85 ± 8.13	0.231
		BSSBP-SYS120′	9 ± 12.22	0.021
		BSSBP-SYS180′	4.77 ± 18.68	0.376
		BSSBP-SYS240′	4.08 ± 14.68	0.337
	Diastolic BP	BSDBP-DIA30′	4.31 ± 5.56	0.128
		BSDBP-DIA60′	3.15 ± 7.05	0.133
		BSDBP-DIA120′	4.69 ± 10.69	0.140
		BSDBP-DIA180′	2.69 ± 11.07	0.398
		BSDBP-DIA240′	1.92 ± 10.95	0.538

(Group 1, level of injury at or above T5; group 2, level of injury below T5). BSSBP = baseline sitting systolic blood pressure; BSDBP = baseline sitting diastolic blood pressure; SYS = systolic; DIA = diastolic; SD = standard deviation

Table 3 Changes recorded in blood pressure after administration of sildenafil (Viagra®) at 30, 60, 120, 180 and 240 min by spasticity grade (according to the modified Ashworth spasticity grade: grade 0; grade 1; grade 2; grade 3; grade 4)

Grade		BP recording	Mean BP difference ± SD	Significance level (P < 0.05)
0	Systolic BP	BSSBP-SYS30′	9.4 ± 10.1	0.128
		BSSBP-SYS60′	6.8 ± 6.26	0.072
		BSSBP-SYS120′	8.4 ± 4.39	0.013
		BSSBP-SYS180′	10 ± 10.07	0.091
		BSSBP-SYS240′	5.2 ± 10.75	0.341
	Diastolic BP	BSDBP-DIA30′	5.8 ± 5.02	0.061
		BSDBP-DIA60′	3.2 ± 2.95	0.72
		BSDBP-DIA120′	6.4 ± 2.41	0.004
		BSDBP-DIA180′	6 ± 7.51	0.149
		BSDBP-DIA240′	1.4 ± 6.54	0.657
1	Systolic BP	BSSBP-SYS30′	16 ± 18.05	0.119
		BSSBP-SYS60′	18.4 ± 19.66	0.1.5
		BSSBP-SYS120′	24.8 ± 22.63	0.070
		BSSBP-SYS180′	20.4 ± 27.94	0.178
		BSSBP-SYS240′	19.8 ± 27.58	0.184
	Diastolic BP	BSDBP-DIA30′	14.2 ± 18.88	0.168
		BSDBP-DIA60′	17.6 ± 17.7	0.90
		BSDBP-DIA120′	16 ± 25.38	0.232
		BSDBP-DIA180′	14.2 ± 23.3	0.245
		BSDBP-DIA240′	13.8 ± 20.68	0.210
2	Systolic BP	BSSBP-SYS30′	5.29 ± 22.08	0.550
		BSSBP-SYS60′	13.86 ± 24.74	0.189
		BSSBP-SYS120′	18.29 ± 21.33	0.064
		BSSBP-SYS180′	5.71 ± 20.58	0.490
		BSSBP-SYS240′	13.86 ± 26.36	0.214
	Diastolic BP	BSDBP-DIA30′	6.86 ± 11.34	0.161
		BSDBP-DIA60′	12 ± 14.44	0.070
		BSDBP-DIA120′	8.71 ± 6.82	0.015
		BSDBP-DIA180′	11.71 ± 7.36	0.006
		BSDBP-DIA240′	13.71 ± 14.6	0.047
3	Systolic BP	BSSBP-SYS30′	−0.6 ± 13.12	0.924
		BSSBP-SYS60′	1.2 ± 8.87	0.777
		BSSBP-SYS120′	11.4 ± 8.87	0.045
		BSSBP-SYS180′	11.6 ± 18.9	0.242
		BSSBP-SYS240′	5.6 ± 11.32	0.331
	Diastolic BP	BSDBP-DIA30′	−5.4 ± 17.92	0.537
		BSDBP-DIA60′	−0.2 ± 8.64	0.961
		BSDBP-DIA120′	4.2 ± 11.47	0.459
		BSDBP-DIA180′	−0.8 ± 2.95	0.577
		BSDBP-DIA240′	−0.6 ± 4.82	0.795

BSSBP = baseline sitting systolic blood pressure; BSDBP = baseline sitting diastolic blood pressure; SYS = systolic; DIA = diastolic; SD = standard deviation

The maximum difference in mean blood pressures in each group was 19.58 mmHg in systolic blood pressure and 13.75 mmHg in diastolic blood pressure, both at 120 min of administration in the complete injury patient group; while in the incomplete injury patient group, the difference was 11.60 mmHg in systolic blood pressure at 120 min and 4.80 mmHg in diastolic blood pressure at 180 min. There was a significant decrease in blood pressure ($P < 0.05$) on all measurements in complete injury patients, while in incomplete injury patients, in spite of decreases in both mean systolic and diastolic blood pressures, the differences did not attain the specified statistical significance ($P > 0.05$) (Table 4).

Duration of injury
The same analysis was performed by dividing the patients into three groups according to duration of injury: group 1, < 18 months with 10 patients (45.45%) group 2, between 18 and 141 months with six patients (27.27%) and group 3, more than 142 months since injury with six patients (27.27%). However, no decrease

Table 4 Changes recorded in blood pressure after administration of sildenafil (Viagra®) at 30, 60, 120, 180 and 240 min by degree of complexity of SCI (according to the ASIA impairment scale: group 1, complete spinal cord injuries – grade A; group 2, incomplete spinal cord injuries – grades B, C, D)

Grade		BP recording	Mean BP difference ± SD	Significance level (P < 0.05)
1	Systolic BP	BSSBP-SYS30′	12.08 ± 19.22	0.052
		BSSBP-SYS60′	14.25 ± 20.68	0.036
		BSSBP-SYS120′	19.58 ± 19.28	0.005
		BSSBP-SYS180′	18 ± 19.74	0.009
		BSSBP-SYS240′	16.08 ± 25.12	0.049
	Diastolic BP	BSDBP-DIA30′	12 ± 12.19	0.006
		BSDBP-DIA60′	12.67 ± 12.36	0.005
		BSDBP-DIA120′	13.75 ± 10.19	0.001
		BSDBP-DIA180′	10.92 ± 11.59	0.008
		BSDBP-DIA240′	11.33 ± 16.33	0.035
2	Systolic BP	BSSBP-SYS30′	1.6 ± 12.82	0.702
		BSSBP-SYS60′	5.8 ± 12.87	0.188
		BSSBP-SYS120′	11.6 ± 13.12	0.021
		BSSBP-SYS180′	3.4 ± 17.29	0.550
		BSSBP-SYS240′	5.7 ± 12.53	0.184
	Diastolic BP	BSDBP-DIA30′	−2.3 ± 14.22	0.621
		BSDBP-DIA60′	3.5 ± 13.81	0.444
		BSDBP-DIA120′	2.9 ± 14.96	0.555
		BSDBP-DIA180′	4.8 ± 14.02	0.307
		BSDBP-DIA240′	3.3 ± 10.27	0.336

BSSBP = baseline sitting systolic blood pressure; BSDBP = baseline sitting diastolic blood pressure; SYS = systolic; DIA = diastolic; SD = standard deviation

in systolic or diastolic blood pressure was observed with sufficient statistical significance ($P < 0.05$), in spite of the fact that decreases were observed in all groups.

Age on injury
Finally, the changes in blood pressure were assessed according to patient age on enrollment in the study by establishing three groups: group 1, age < 30 years, with nine patients (40.91 %); group 2, age between 30 and 40 years, with seven patients (31.82%); and group 3, age over 40 years, with six patients (27.27%). The differences observed in blood pressure also did not show statistically significant decreases in this analysis, although a greater tendency to hypotension was noted in older patients than in younger patients.

Adverse effects
With regard to the adverse effects observed during the study, five patients (22.73%) had manifestations considered as adverse effects: three patients (13.64%) showed facial flushing (subjective sensation of facial warmth felt by the patient), one patient had facial erythema (4.55%) and one other patient had facial erythema and pruritus (4.55%). These adverse effects were transient and well tolerated. None of the patients had clinical symptoms or signs compatible with hypotension.

Discussion

It was not the purpose of this study to test the efficacy of a drug, which has been tested on various occasions for the treatment of ED in SCI patients with very good results.[2,6–8,15,16] Such was the case that the monitoring of blood pressure and other side effects was performed in a setting lacking sexual stimuli. Neither the time or the site of the study were suitable for reliable assessments of efficacy.

In the multicenter study carried out by Sánchez Ramos et al,[2] in which this unit participated, an 88.2% improvement in ED secondary to SCI was obtained with the use of sildenafil (Viagra®). Of the 170 patients entered in that study, side effects were reported in 41 patients, but none were directly related to hypotension events. We should remember, however, that patients with hypotension (blood pressure ≤ 90/50 mmHg) were excluded from this study.

Similarly, when Derry et al[6] studied the efficacy and safety of oral sildenafil (Viagra®) in male patients with ED caused by SCI, they excluded patients with a neurologic level of injury above T5. The same criteria were also established in the studies by Maytom et al[7] and Schmid et al.[15] However, Gans et al[13] conducted a study on the efficacy and safety of sildenafil in SCI patients and reported a case of treatment withdrawal due to hypotension. No other study reported significant changes in blood pressure.

We should remember that the distribution of SCI patients according to level of injury varies little from one author to another and can be established as 50.7% cervical, 35.1% thoracic and 11.0% lumbosacral.[22] As a result of this systematic exclusion of patients with injury levels above T5, this very effective treatment for ED is not used in over half of the SCI patients.

On the other hand, hypotension is a very common finding in patients with SCI, although a commonly accepted value for its incidence cannot be established. This leads to the exclusion of many individuals with SCI from the use of sildenafil (Viagra®) as treatment for ED.

These two facts led us to question the appropriateness of maintaining these exclusion criteria on a general basis. This is what prompted us to conduct this study, which aims to standardize the protocol used in our SCI Unit and to subject all patients in whom all other previously described contraindications are excluded to a test of tolerance (but not of efficacy) to sildenafil. This test will be performed as described in this study by monitoring the patient's blood pressure in the hospital for 4 h after administration of 50 mg of sildenafil (Viagra®) and recording all events occurring during this period.

An aspect that should be considered with regard to the potential risk of inducing hypotension in an SCI patient treated with sildenafil is that the activity for which this treatment is indicated is usually performed when the patient is in a supine position, which has a hypertensive effect that would compensate for this risk.

In this study, treatment of ED with sildenafil (Viagra®) in SCI patients caused a comparatively larger blood pressure reduction in patients with a neurologic level at T5 or above compared to those who had a neurologic level below T5. However, symptoms compatible with hypotension were not detected in any patient. It should be taken into account that these patients usually have decreased blood pressure levels that are lower than reference levels. This may help to increase their tolerance of hypotension and cause more rapid activation of compensatory mechanisms. This fact would allow administration of sildenafil to tetraplegic patients, regardless of their level of SCI. This study, in which blood pressure was monitored with the patient sitting at 45° without sexual activity, did not detect any episode of symptomatic hypotension. The change to a supine position and combination with sexual activity should constitute a safeguard against symptomatic falls in blood pressure.

The presence of spasticity in SCI patients has an estimated incidence of 67–78%[17] and its prevalence has been established at 68%. In addition, it has been noted that it is more frequent in cervical and incomplete injuries.[17] Its harmful effects are well known, but so also its ability to improve specific aspects of the patient who develops it. An increase in muscle tone can control the decrease in blood pressure and minimize the effect of orthostatic hypotension. For this reason, we attempted to establish a relationship between the decrease in blood pressure following administration of sildenafil (Viagra®) and the presence of a certain grade of spasticity. Based on the results obtained, we can conclude that high grades of spasticity are protective against the tendency to a decrease in blood pressure following administration of sildenafil (Viagra®). In fact, the group of patients with grade 3 spasticity was the one in which the tendency to hypotension had the least statistical significance. In some patients, an elevation of blood pressure versus baseline values was even detected. It would therefore be recommendable that other studies be conducted focusing on this aspect.

It should be noted that baseline blood pressure values were very similar in the two groups, and even slightly higher in patients with a level of SCI injury above T5. This paradoxical situation is explained by the greater percentage of patients with higher grades of spasticity in group 1 than in the group with lower levels of SCI (Table 1).

Complexity of the SCI appeared to be related to the hypotensive tendency detected after administration of sildenafil (Viagra®). However, the patient group with grade A complete injuries did not show any clinically significant symptoms compared to those with incomplete injury grades (B, C and D). We did not expect to find any changes related to patient age at the time of performance of the test or duration of ED, as in fact occurred.

When the mean decreases in systolic and diastolic blood pressure were assessed in the overall patient group, the maximum decreases were found to occur at 90 min for both measurements. However, when the changes were assessed according to the level of injury and complexity, where the fall in blood pressure was significant, the maximum decrease appeared about 120 min after administration of sildenafil (Viagra®).

The percentage and characteristics of the side effects observed did not differ significantly from those found in the different studies reviewed.[2,6–8,15,16]

Conclusions

Administration of 50 mg of sildenafil (Viagra®) causes a decrease in blood pressure in all patients with ED secondary to SCI. This decrease is more significant ($P < 0.05$) in patients with a neurologic level of injury at or above T5. It is also more significant ($P < 0.05$) in patients with grade A SCI on the ASIA impairment scale. However, signs or symptoms of hypotension were not detected in any patient.

Spasticity acts as a protective factor against the potential lowering of blood pressure values caused by sildenafil (Viagra®). This protective effect is more evident the higher the grade of spasticity.

Hospital protocolization of a test for monitoring blood pressure after administration of sildenafil to patients with ED secondary to SCI may allow this treatment to be administered more safely in individuals with hypotension and/or a neurologic level of injury above T5.

A larger study conducted in a greater number of patients with higher doses of sildenafil would yield further relevant information on the current restrictions for the use of this medication in patients with neurologic injuries above T5 and asymptomatic hypotension.

References

1 NIH Consensus Development Panel on Impotence. Impotence. *JAMA* 1993; **270:** 83–90.

2 Sánchez Ramos A *et al*. Efficacy, safety and predictive factors of therapeutic success with sildenafil for erectile dysfunction in patients with different spinal cord injuries. *Spinal Cord* 2001; **39:** 637–643.

3 Goldstein I *et al*. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl Med* 1998; **338:** 1397–1404.

4 Morales A *et al*. Clinical safety of oral sildenafil citrate (Viagra®) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; **10:** 69–74.

5 Padma-Nathan H *et al*. Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Sildenafil Study Group. *Int J Clin Pract* 1998; **52:** 375–379.

6 Derry FA *et al*. Efficacy and safety of oral sildenafil (Viagra®) in men with erectile dysfunction caused by spinal cord injury. *Neurology* 1998; **51:** 1629–1633.

7 Maytom MC *et al*. A two-part pilot study of sildenafilo (Viagra®) in men with erectile dysfunction caused by spinal cord injury. *Spinal Cord* 1999; **37:** 110–116.

8 Guliano F *et al*. Randomized trial of sildenafil for the treatment of erectile dysfunction in spinal cord injury. *Ann Neurol* 1999; **46:** 15–21.

9 Andersson KE, Wagner G. Physiology of penile erection. *Biol Reprod* 1995; **75:** 191–236.

10 Burnett AL. The role of nitric oxide in the physiology of erection. *Biol Reprod* 1995; **52:** 485–489.

11 Boolell M *et al*. Sildenafil. An oral active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treat-ment of penile erectile dysfunction. *Int J Impot Res* 1996; **8:** 47–52.

12 Arcoraci C, Orellano S, Discepolo M, Ribs R. Tratamiento de la disfuncion erectil sexual con sildenafilo en pacientes con hemodialisis e interaccion con las drogas hipertensivas. *Rev Nefrol Dial y Transpl* 2000; **50:** 29–31.

13 Gans WH *et al*. Efficacy and safety of oral sildenafil in men with erectile dysfunction and spinal cord injury. *J Spinal Cord Med* 2001; **24:** 35–40.

14 Rosen RC *et al*. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49:** 822–830.

15 Schmid DIVI, Schurch B, Hauri D. Sildenafil in the treatment of sexual dysfunction in spinal cord-injuried male patients. *Eur Urol* 2000; **38:** 184–193.

16 Derry F, Hultling C, Seftel AD, Sipski ML. Efficacy and safety of sildenafil citrate (Viagra®) in men with erectile dysfunction and spinal cord injury: a review. *Urology* 2002; **60**(suppl)**:** 49–57.

17 Maynard FM, Karunas R, Waring WW. Epidemiology of spasticity following traumatic spinal cord injury. *Arch Phys Med Rehabil* 1990; **71:** 566–569.

18 Levi R, Hulting C, Seiger A. The Stockholm Spinal Cord Injury Study: 2. Associations between clinical patient characteristics and post-acute medical problems. *Paraplegia* 1995; **33:** 585–594.

19 Ignarro LJ *et al*. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for involvement of *S*-nitrosothiols as active intermediates. *J Pharmacol Exp Ther* 1981; **218:** 739–749.

20 Lugnier C, Komas N. Modulation of vascular cyclic nucleotide phosphodiesterases by cyclic GMP: role in vasodilatation. *Eur Heart 3* 1993; **14**(suppl 1)**:** 141–148.

21 Bohannon RW, Mellissa BS. Interater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1985; **65:** 46–47.

22 DeVivo M. Epidemiology of traumatic spinal cord injury. In: Kirshblum S, Campagnolo DI, DeLisa JA (eds). *Spinal Cord Medicine*. Lippincott Williams and Wilkins: Philadelphia 2002, pp 69–81.