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Original Article

Time/duration effectiveness of sildenafil *versus* tadalafil in the treatment of erectile dysfunction in male spinal cord-injured patients

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Study design: A randomized, blinded, crossover clinical trial comparing sildenafil *versus* tadalafil for erectile dysfunction (ED) in male spinal cord-injured (SCI) patients.
Objectives: To compare the safety, time/duration effectiveness, and the impact on the quality of life (QoL) of tadalafil 10 mg versus sildenafil 50 mg.
Setting: Neurourology Section, Careggi Hospital, Florence, Italy.
Methods: During a screening (visit 1), a diary card was distributed, in which the subjects assessed, after each attempt at intercourse the quality of their erection, responding (*Yes*/*No*) to both Sexual Encounter Profile Questions 2 (SEP2) and 3 (SEP3). The subjects made at least four attempts at intercourse. At visit 2, 15 patients (group 1) were assigned sildenafil and 15 (group 2) started with tadalafil. Responses to baseline International Index of Erectile Function 5 items (IIEF-5), Questions 13–14 (IIEF 15 items) and SEP diary were recorded. Patients attempted intercourse on four separate occasions: within 4 h of taking the first tablet, within 12 h for the second tablet, 24 h for the third, and the fourth from 24 to 36 h. At visit 3, the investigators evaluated the effectiveness with the same measures used at baseline. After a wash-out period, at visit 4, Group 1 was given tadalafil, and Group 2 was given sildenafil. Patients were required to observe the same criteria in taking the four tablets as in visit 2. After 4 weeks (visit 5), we evaluated the patients as we did in visit 3.
Results: Overall, 28 patients completed the study. No subjects discontinued the drugs due to drawbacks.
Tadalafil allowed a majority of men in this trial to achieve both normal sexual functioning up to 24 h postdosing compared to sildenafil ($P<0.01$) and improved overall sex life satisfaction as well as sexual relations with partner.
Conclusion: Based on these data, tadalafil may have the potential to become an important treatment option for ED in SCI patients.
Sponsorship: This study was not sponsored.
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Keywords: erectile dysfunction; spinal cord injury; phosphodiesterase type5 inhibitors

Introduction

Sildenafil, a phosphodiesterase-(PDE)-5-selective inhibitor, has been the drug of choice for spinal cord injury (SCI) patients with erectile dysfunction (ED) since it was launched in March 1998.[1,2] Either or both psychogenic (nonsomesthetic supraspinally elicited) and reflexive (somesthetic spinally elicited) erections, confirmed by urodynamic and electrophysiologic findings, are necessary for response to sildenafil therapy.[3] In addition, sildenafil due to the positive effect on the quality of a partnership showed long-term compliance compared to invasive treatment such as intracavernosal injection of alprostadil.[4,5] The evaluation of QoL of the couple with regard to treatment is fundamental considering that often in SCI patients pharmacotherapy becomes a pharmacoprosthesis as SCI patients need to use a continued therapy in order to achieve a satisfactory erection.

A recent review of the efficacy and safety of sildenafil treatment for ED in men with SCI reported improved erections and up to 72% of intercourse attempts were successful;[6] combined with significantly enhanced key QoL parameters regardless of the cause of lesion, neurological level, assessed on the criteria of the American Spinal Injury Association (ASIA) scale,[7] and time since injury. Despite its proven clinical efficacy

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in SCI patients, however, literature reports that those patients in treatment with sildenafil may stop taking this drug after a brief period if they are unsatisfied in terms of QoL due to the unpredictable time delayed action, and in some cases due to the inefficacy of the drug. Moreover, Gallery *et al*[8] reported a possible tachyphylaxis effect with sildenafil. Of the patients studied for 2 years, 20% had to increase the sildenafil dose in order to continue to achieve the same effect. Alternative treatment such as sublingual apomorphine hydrochloride was not overly investigated in SCI men because literature has reported a low response rate for the treatment of erectile dysfunction in those patients suggesting apomorphine as nonvaluable therapy for erectile dysfunction in SCI patients.[9] Our experience with apomorphine showed that only patients with a slight neurological defect (Frankel D) may respond to apomorphine.[10] Selective inhibition of PDE5 is a rational therapeutic approach in ED, as proved by the clinical success of sildenafil. Tadalafil is one of the two new PDE5 inhibitors now approved for use in the European Union and other countries.[11–13] Clinical trials conducted to date across a large population of men with ED of various causes demonstrate that tadalafil is effective and safe in treating ED. There are few studies directly comparing sildenafil to other PDE5 inhibitor treatments for ED.[14] Most studies have compared tadalafil only to a placebo, so whether tadalafil presents advantages over sildenafil has yet to be seen. According to studies conducted to date, side effects produced by tadalafil were generally mild-to-moderate, in particular no abnormal visual effects, and no clinically significant changes in blood pressure or electrocardiographic parameters were observed. Tadalafil achieves maximum plasma concentrations within 2 h and has a mean terminal half-life of 17.5 h; with adequate sexual stimulation, significant erectile responses have been observed as early as 16 min and as long as 36 h after dosing in about 50% of men with ED.[15] One possible advantage is that, given such a broad period of responsiveness, patients and their partners may not need to 'time' or 'synchronize' their sexual activities according to dosing. That could be relevant if female partners are particularly reluctant to 'plan' sexual activity. On the other hand, in our experience,[16] SCI patients using sildenafil reported the ability to have sexual intercourse successfully two or more times within 24 h of dosing, and consequently, we advised our patients to make multiple attempts for up to 24 h without taking another tablet. Recently, Moncada *et al*[17] reported that of the total 40 patients 74% reported a successful erection 12 h after the intake of the drug, so it would be likely that the inhibition of the PDE5 activity that sildenafil caused should be much longer lasting than the half-life of the drug in the blood, and so the duration of action of sildenafil is not well-known. Although various studies reported the undoubtedly superior pharmacokinetic properties of tadalafil compared to other PDE5 inhibitors such as sildenafil and vardenafil in men, these findings should be interpreted with caution, because at this time it is unclear how much of a positive impact the pharmacokinetic profile could have on clinical effectiveness, especially in SCI patients. Even if tadalafil is consistently efficacious across disease severities and etiologies, as well as in patients of all ages, it is not known at this time if tadalafil is effective in patients with spinal cord injuries suffering from ED as they have either been excluded or are poorly represented in clinical trials.

We compared the safety, efficacy and the impact of QoL correlated to the treatments of tadalafil 10 mg *versus* sildenafil 50 mg in SCI patients. We analyzed the data of SEP diaries obtained with the two drugs using the χ^2 test for each time segment: 1–4, 4–12, 12–24, 24–36 h. $P<0.05$ was set as the criterion for a significant difference.

Methods

Visit 1 We screened in 4 weeks, 30 SCI patients, aged 21–60 (mean age 34. 6 years) with ED due to a traumatic event.

Inclusion criteria

Time since injury ranged from a minimum of 6 months to a maximum of 1 year. None of them had ED prior to neurologic impairment and none used nitrate or anticoagulant therapies prior to screening. No subjects had used any medication for ED. Patients had to be involved in a stable relationship.

Exclusion criteria

All patients with history of stroke, subarachnoid hemorrhage, bleeding disorders or active peptic ulceration and those with severe renal insufficiency (creatinine clearance <30 ml/min), severe hepatic insufficiency, patients with diabetes mellitus or with abnormal hormone profile: FSH, LH, PRL, testosterone, known at the time of screening or based on tests performed at visit 1, and subjects who were clinically depressed. We excluded patients with genital anatomical deformities; spinal cord lesioned (SCL) men who drank more than 28 units of alcohol per week. Also excluded from the study were SCL individuals not responding to an intracavernous injection test of alprostadil at 10 μg, which prompted suspicion of a vascular reason for ED.

Subjects who developed symptomatic, active urinary tract infection could be enrolled after receiving appropriate antibiotic therapy.

All participants provided written informed consent before enrollment and the study was conducted in accordance with the Declaration of Helsinki.

The patients were divided into groups with regards to level of lesion and the degree of spinal cord lesion assessed on the criteria of the American Spinal Injury Association (ASIA) impairment scale (Table 1).

During a 4-week treatment-free, run-in period the subjects were to make at least four attempts at

Table 1 Degree of spinal cord lesion according to ASIA scale

	Frankel		
	A	*B*	*D*
Cervical lesion	4	2	3
Dorsal lesion above D10	6	0	0
Dorsal lesion below D10	7	5	3

intercourse on four separate days. At visits 1–4, a subject diary was dispensed to the patient to allow collection of data for the period between visits. In this diary, the subjects recorded the date and time when sexual activity was attempted assessing after each attempt at intercourse the efficacy of their spontaneous erection, responding (*Yes*/*No*) to Sexual Encounter Profile Question (SEP2) regarding penetration: 'Were you able to insert your penis into your partner's vagina?' while for erection maintenance responding (*Yes*/*No*) to SEP3: 'Did your erection last long enough for you to complete intercourse?' The data of SEP diaries were assessed by investigators. Adverse events (AEs) were recorded by the investigators throughout the study with nonleading questions.

Patients were included in visit 2 if at least 50% of their sexual intercourse attempts during the untreated period were unsuccessful according to SEP2 and SEP3, the IIEF(5) score was lower than 21, and if they responded to the hematologic examinations required according to the criteria above mentioned.

We determined the severity of ED using the International Index of Erectile Function IIEF(5).[18] Moreover, all patients answered the IIEF questions (13 and 14) of the 15-item International Index of Erectile Function (IIEF) regarding the impact of the drugs in terms of QoL. Patients were randomized by means of a computer generated table in two groups. Group 1 was assigned to start with sildenafil and Group 2 with tadalafil. Men were given either four doses of sildenafil 50 mg or four doses of tadalafil 10 mg. In both cases, the sildenafil and the tadalafil tablets were placed in an opaque gelatine capsule.

Both groups were asked to attempt intercourse on four separate occasions: within 4 h of taking the first tablet, within 12 h for the second tablet, 24 h for the third and from 24 to 36 h after the fourth tablet. They agreed to attempt at least four sexual encounters during a period of 28 days and to fill in the SEP diaries only at the first attempt to have sexual intercourse for each time segment 1–4, 4–12, 12–24, 24–36 h.

To be included in visit 3, patients had to have made attempts at sexual intercourse on all four separate occasions and they had to have completed all the diary entries.

Several measures were used to assess erectile function: IIEF (5) comparing the scores obtained from baseline both by IIEF (5) and by means of Sexual Encounter Profile (questions 2 and 3) defined as, respectively, the success of insertion and maintenance of erection (YES responses) after each attempt compared to baseline. The QoL evaluated compared the scores obtained responding to questions 13 and 14 of IIEF-15 at baseline and after drug treatments.

After a wash-out period of 2 weeks in visit 4, Group 1 received tadalafil, and Group 2 sildenafil. SCI patients had to observe the same criteria in taking the four tablets on four different occasions as in visit 2. They had to fill in and complete a new SEP diary.

Visit 5 The evaluation of the effectiveness was the same as that of visit 3 (Figure 1).

Results

Out of 30 patients, 28 (93.3%) completed the study. We did not observe in any patient an adverse event correlated to either drug. One patient randomized to the sildenafil group was lost, as well as 1 patient randomized to the tadalafil group, that is, they did not appear at visit 3. Therefore, these two patients were not included in the analysis of results.

The mean score of IIEF (5) at the baseline was: 11.25 (range 8–13), while for the overall satisfaction with sex life question 13 of IIEF, we obtained a mean score of 1.61 (range 1–3) and regarding sexual relations with partner question 14 (IIEF 14), we detected a mean score of 1.54 (range 1–3).

The IIEF (5) reached a mean score with sildenafil of 15.75 (range 10–18) with an increase over baseline of 40%. Five patients reported consistent unsuccessful intercourse with sildenafil: one with complete upper motoneuron lesion (UMN) dorsal D6 and four with lower motoneuron lesion (LMN), of which one incomplete Frankel B and one Frankel C. Regarding the impact on QoL the mean score increased from baseline by 84.44% for Q13: mean score: 2.96 (range 1–5) and 76.74% for Q14: 2.71 (range 1–5). The mean score of IIEF (5) obtained with tadalafil was 17.82 (range 10–21) increasing from baseline by 58.41 and 13.15% from sildenafil (Figure 2). Tadalafil significantly increased the percentage of successful intercourse attempts at 24 h $P<0.01$: 19 out of 28 patients (67.9%), compared to five out of 28 patients (17.9%) with sildenafil, while we did not observe a significant difference in up to 12 h. After 24–36 h postdose nine out of 28 patients (32.14%) responded Yes to SEP 2 and SEP 3 with tadalafil compared to two out of 28 patients (7.14%) with sildenafil. However, the number of responders in the two groups is not large enough to consider the χ^2 test statistically significant (Figure 3).

Three patients did not respond to either drug, while the two patients with LMN incomplete responded only to tadalafil. The mean score for Q13 was 3.46 (range 1–5) and for Q14 was 3.71 (range 1–5) with an increase over baseline of 115.56% (Q13) and 141.86% (Q14). Improvement of tadalafil versus sildenafil was, respectively, 16.86% for Q13 and 36.84% regarding Q14 (Figure 4).

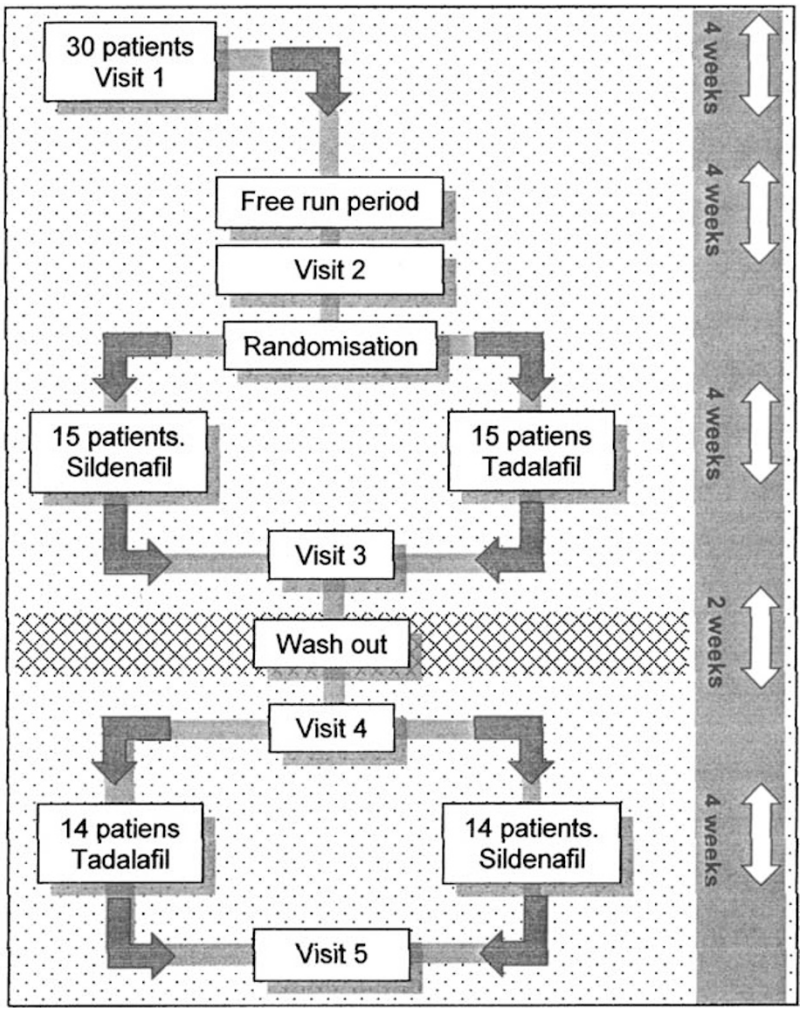

Figure 1 Study design

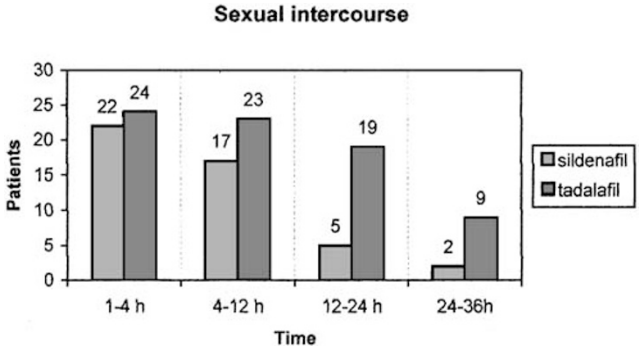

Figure 2 Time/duration effectiveness of sildenafil *versus* tadalafil

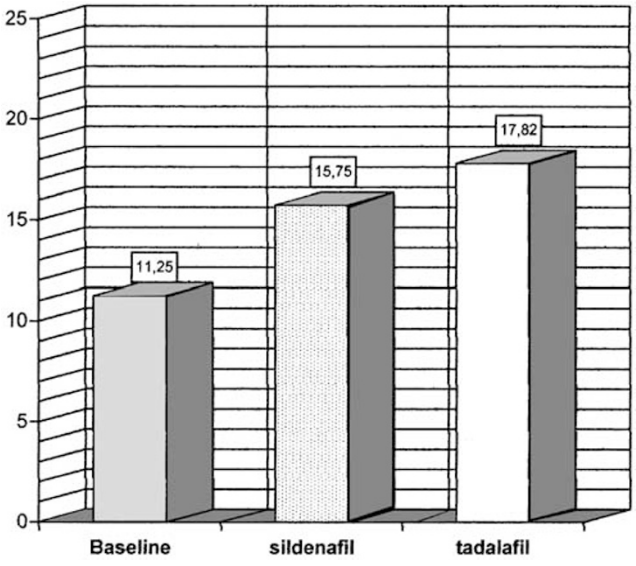

Figure 3 Mean maximum IIEF scores were achieved with tadalafil

Conclusion

We determined that tadalafil allowed a majority of men in this trial to achieve normal sexual functioning at up to 12–24 h after taking the drug compared to sildenafil. The

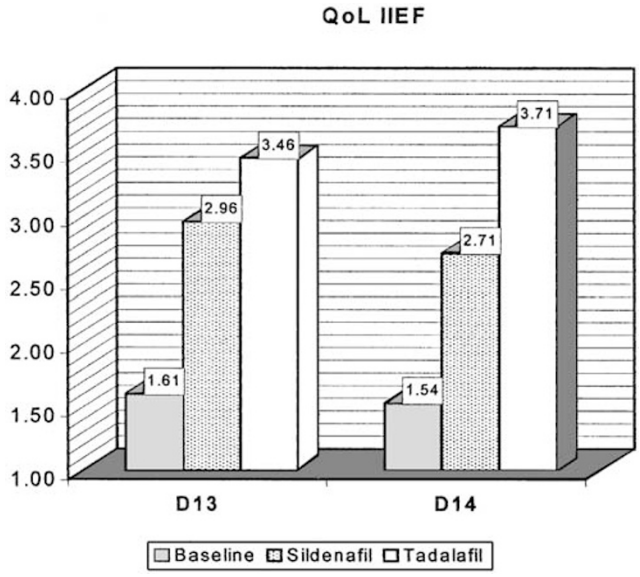

Figure 4 Mean maximum scores regarding Q13 and Q14 were obtained with tadalafil

extended duration of responsiveness may help eliminate the need for planning sexual intimacy, could potentially set new expectations in the treatment of ED in SCI patients suffering from ED and explain why patients showed positive feedback in terms of QoL related to the treatment. Based on these data, tadalafil may have the potential to become an important treatment option for ED in SCI patients. The development of the new PDE-5 inhibitors prompts the question of whether and how these three substances differ in terms of their efficacy and adverse effects for a specific category of ED, including SCI patients, allowing the best choice from these oral drugs.[19]

Our results showed that the advantage of tadalafil over sildenafil in terms of duration of action was not influenced by level or degree of lesions in SCI men. In our study, two out of five patients (40%) not responding to sildenafil, all with LMN from lumbar incomplete lesions with minimum preservation of reflexive erection, reported to be satisfied after sexual intercourse using tadalafil. Further investigation with a long-term follow-up is needed to know if tadalafil may have a better impact than sildenafil in SCI patients with LMN in which reflexive erection is partial or absent. It is well known that the mean effectiveness of sildenafil in this kind of patient is about 50%.

There are no studies, at this time about efficient alternative oral therapy for ED in SCI patients not responding to sildenafil. Tadalafil seems to be the only potential therapeutic option in SCI patients not responding to sildenafil. According to recent data, it is obvious that the concept of PDE-5 inhibition has a central position in oral pharmacotherapy of ED. However, larger clinical studies of efficacy and safety of these agents should be carried out with SCI men, using most of the other above-mentioned oral drugs, to investigate the possible role of the new PDE-5 inhibitors as a therapeutic effect in regaining spontaneous satisfactory erections in SCI patients too.

As yet, insufficient data are available to evaluate the adverse effects of tadalafil, particularly its long-term use and use in high-risk groups. Sildenafil has already been used by over 20 million men in over 110 countries and is one of the best-studied pharmacological substances available. This advantage in terms of knowledge and safety data makes sildenafil a safe and reliable treatment for patients with ED due to spinal cord lesions. Before considering tadalafil as the first-line therapy with an acceptable risk–benefit ratio, additional information is necessary to clarify any possible risks associated with tadalafil in such patients. By means of long-term treatment, we can observe or exclude a possible tachyphylaxis effect of tadalafil, forcing patients to increase the dosage in order to have the same effect, and/or detecting any adverse effects and possible negative results with other unrelated drugs. Furthermore, in prescribing a therapy for ED, it is important to understand the needs of the couple; a long-lasting therapy may not be the most important factor in their choice. On the other hand, it must be assessed if the early use of a long-acting therapy just after spinal shock phase may favor the maintenance of corpora cavernosae functions and the recovery of spontaneous erections in SCI patients.

Acknowledgements

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