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Original Article

Phosphodiesterase inhibitors in the treatment of erectile dysfunction in spinal cord-injured men

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Study design: Open, before–after study.
Objective: To assess the efficacy and safety of phosphodiesterase type 5 (PDE5) inhibitors for erectile dysfunction (ED) in spinal cord-injured (SCI) patients.
Setting: Home- and clinic-based assessments in the outpatient department at the Centre Bouffard Vercelli, Cerbère France.
Methods: Clinic trials with Sildenafil (Viagra®) on 120 patients, Tadalafil (Cialis®) on 54 patients and Vardenafil (Levitra®) on 66 patients were performed. Flexible doses of PDE5 inhibitors were given depending on efficacy and tolerability, from 50 to 100 mg for Sildenafil, and from 10 to 20 mg for Vardenafil and Tadalafil. Each trial was performed after a week's interval. The efficacy was self-assessed by the patients on a six-point quantitative scale assessment. The response to treatment was assessed at home in 90 patients (57 patients on Sildenafil, 12 patients on Vardenafil and 21 patients on Tadalafil) using the International Index of Erectile Function (IIEF).
Results: In clinic trials, PDE5 inhibitors were effective (rigidity enough for penetration) in 85% of the patients on Sildenafil, 74% of the patients on Vardenafil and 72% of the patients on Tadalafil. The mean duration of erection was 34, 28 and 26 min, respectively. Adverse effects were mild, usually attenuated with continued dosing. More than 70% of the patients on Vardenafil and Tadalafil required higher doses of 20 mg, whereas 50 mg of Sildenafil was effective in 55% of the patients. Two-thirds of our patients on Tadalafil reported a duration of action longer than 24 h. The presence of an upper motor neuron lesion was significantly associated with therapeutic success, lower motor neuron lesions and cauda equina patients were poor responders. Other variables such as completeness of lesion had no impact.
In the follow-up visits, the IIEF global scores and three IIEF domains (erectile function, intercourse satisfaction and overall satisfaction) were significantly improved in all patients. Patients on Sildenafil showed a significant improvement of orgasmic function, ejaculation (Question 9) and orgasm (Question 10).
Conclusion: Sildenafil, Vardenafil and Tadalafil are all effective and well-tolerated treatments for ED in SCI patients. Although no statistical analysis could be applied on these data, these results might indicate that Sildenafil is more effective in treating ED. Clinic trials are important for proper dose titration and appropriate education of the patients.
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Keywords: spinal cord injury; erectile dysfunction; ejaculation; Sildenafil; Vardenafil; Tadalafil

Introduction

Erectile dysfunction (ED) is a common consequence of spinal cord injury (SCI). Several studies showed that 48–92% of SCI patients could achieve erection – depending upon the definition of erection by the authors. Both the type and level of SCI can affect the extent of ED. Patients with incomplete lesions, upper motor neuron lesion and higher cord lesions are more likely to recover erectile responses. However, these erections are frequently unsuitable for satisfactory sexual activity.[1–5]

Intracavernous injections of vasoactive drugs (such as papaverine, prostaglandin E1 or alpha-blocking agents) have constituted the first effective pharmacological

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management of dyserection in SCI patients. Their side effects (priapism and fibrosis of the corporal tissue) and the injection therapy, which can be unacceptable to some men, can limit their use.[3,6,7]

Sildenafil (Viagra®) has represented the first effective oral drug that promotes erection in neurogenic and non-neurogenic patients, and it has been followed recently by two newer drugs, Vardenafil (Levitra®) and Tadalafil (Cialis®). They all have an identical mechanism of action. They promote erection by inducing smooth muscle relaxation in the corpus cavernosum through selective inhibition of phosphodiesterase type 5 (PDE5), and thereby reducing the inactivation of cGMP, which potentiates corporal smooth muscle relaxation. Double-blind, placebo-controlled studies with Sildenafil demonstrated its efficacy in improving sexual function in SCI patients, especially in the quality of erection and satisfaction with sex life.[1,8–11] Studies with Vardenafil and Tadalafil are sparse.[12]

We report our experience in managing ED in SCI patients, with the three available PDE5 inhibitors, in an open study.

Patients and methods

Study design

Between 1999 and 2005, 120 consecutive patients were first treated with Sildenafil, and then 66 patients were treated with Vardenafil and 54 patients with Tadalafil.

The following clinical data of the SCI patients were obtained at baseline: age, duration of SCI, level of lesion, degree of lesion using the ASIA impairment scale and type of lesion. The upper motor neuron refers to injuries that are above the level of the sacral spinal segments; this results in a spastic type of paralysis, with presence of sacral reflexes (bulbocavernosus and/or anal reflexes). Conversely, the lower motor neuron injury refers to an injury affecting the sacral spinal segment.

Trials with PDE5 inhibitors were performed in the outpatient clinic. Each clinic trial consisted of manual sexual simulation (masturbation) 30–60 min after drug intake to achieve the best possible reflexogenic erection. Instructions were given to maintain the erection as long as possible. The patients received the PDE5 inhibitor in flexible doses, starting with 50 mg for Sildenafil, and 10 mg for Vardenafil and Tadalafil. Depending on efficacy and tolerability, the dose was increased after a week's interval, to 100 mg (Sildenafil), and 20 mg (Vardenafil and Tadalafil). Patients on Tadalafil were asked to have another sexual stimulation the day after the intake to assess the duration of action.

If effective, the drug was prescribed for sexual intercourse at home, and the patients were reviewed in a follow-up visit, at least 3 months after the clinic trials.

Patients

All patients suffered a traumatic SCI injury. They were adults of 18 years old or more, involved in a stable relationship with active sexual life despite ED. Patients prone to blood pressure instability were excluded, as well as subjects with known or suspected vascular disease. Further exclusion criteria were cardiovascular diseases, peripheral neuropathy and patients on nitrates drugs or anticoagulants.

Sexual assessments

The baseline assessments included the International Index of Erectile Function (IIEF) questionnaire, the quality and duration of erection.

The severity of ED was determined using the IIEF questionnaire during the 4-week treatment-free period before hospitalization with at least four attempts at intercourse. The IIEF is a brief, reliable, self-administered questionnaire of erectile function validated in 10 languages including French that detects treatment-related changes in patients. It is a 15-item questionnaire that addresses the relevant domains of male sexual function:[13]

- erectile function (Questions 1–5, 15)
- intercourse satisfaction (Questions 6–8)
- orgasmic function (Questions 9 and 10)
- sexual desire (Questions 11 and 12)
- overall satisfaction (Questions 13 and 14).

The quality of the reflexogenic erection was self-assessed by the patients on a six-point quantitative scale from 0 (no erection at all) to 5 (full rigidity). Rigidity equal or superior to 4 was considered hard enough for penetration. The duration of reflexogenic erection was reported by the patients (in min).

In clinic trials, the quality and duration of erection, and the side effects were recorded, together with the duration of action (for Tadalafil only). The IIEF questionnaire was repeated to assess the erectile function at home.

Statistical analysis

Descriptive statistics, including means and SD were calculated to describe characteristics of the population. Analysis of variance (ANOVA) was used to compare the three groups, with ANOVA test and Kruskal–Wallis test for continued and discontinued data, respectively.

Results

Study population

The data for the SCI patients on Sildenafil, Vardenafil and Tadalafil are presented in Table 1. There was a majority of paraplegic patients, of complete lesions (ASIA A) and of upper motor neuron lesions in each group. The three groups were not significantly different in terms of age, duration of SCI, level and type of lesion and ASIA impairment.

Table 1 Characteristics of the population

	Sildenafil (n = *120*)	*Vardenafil* (n = *66*)	*Tadalafil* (n = *54*)	
Age (years)	35.6 (11.2)	36.2 (13.2)	32.6 (11.6)	NS
Duration of SCI (months)	112.4 (8.4)	92.0 (11.2)	91.5 (12.4)	NS
Level of lesion	35 tetraplegics	23 tetraplegics	20 tetraplegics	NS
	78 paraplegics	37 paraplegics	30 paraplegics	
	7 cauda equina	6 cauda equina	4 cauda equina	
ASIA impairment	100 A	53 A	44 A	NS
	8 B	5 B	6 B	
	8 C	7 C	3 C	
	4 D	1 D	1 D	
Type of lesion	110 UMN	56 UMN	47 UMN	NS
	10 LMN	10 LMN	7 LMN	

Mean (SD); UMN: upper motor neuron lesions, LMN: lower motor neuron lesions; NS: nonsignificant difference between the three groups

Table 2 Baseline assessments and efficacy outcome in clinic trials

	Sildenafil (n = *120*)		*Vardenafil* (n = *66*)		*Tadalafil* (n = *54*)		
	Baseline	*Test*	*Baseline*	*Test*	*Baseline*	*Test*	
Rigidity	3.7 (1.1)	4.6* (0.9)	2.8 (1.4)	4.2* (1.1)	3.1 (1.5)	4.1* (1.3)	NS
Duration of Erection (min)	2.8 (2.1)	33.5* (12.2)	1.3 (1.6)	27.7* (25.5)	4.2 (1.9)	25.7* (18.8)	NS
Side Effects	—	15%	—	14%	—	6%	
Optimal dose	—	50 mg: 66	—	10 mg: 14	—	10 mg: 15	
		100 mg: 54		20 mg: 52		20 mg: 39	

Mean (SD)
*Significant difference in each group
NS: nonsignificant difference between the three groups

Baseline sexual assessment
The rigidity of the erection was good (four or five) in 51% of the patients, but of very short duration (less than 3 min). These data were not significantly different in the three groups (Table 2).

The IIEF global score was low, with a mean of $33.8 \pm 7.2/75$. Considering the different domains, erectile function ($14.3 \pm 4.9/30$), intercourse satisfaction ($5.9 \pm 2.1/15$), orgasmic function ($2.6 \pm 1.4/10$) and overall satisfaction ($2.4 \pm 1.1/10$) were all low, but the sexual desire ($8.5 \pm 1.3/10$) remained high. These data were not significantly different in the three groups.

Clinic trials
A good rigidity (four or five) was reported by 85% of the patients on Sildenafil, 74% of the patients on Vardenafil and 72% of the patients on Tadalafil. The mean duration of erection was of 34 min on Sildenafil, 28 min on Vardenafil and 26 min on Tadalafil (Table 2).

Adverse effects were mild, 15% of the patients on Sildenafil reported mainly headache, flush, dizziness and dyspepsia; 14% of the patients on Vardenafil reported mainly headache and dizziness; and 6% of the patients on Tadalafil reported mainly headache and back pain. These effects were usually attenuated with continued dosing. No patient discontinued the treatment because of these side effects.

With Vardenafil and Tadalafil, the initial dose of 10 mg was found ineffective in more than 70% of the patients, whereas 50 mg of Sildenafil was effective in 55% of the patients (Table 2).

Two-third of our patients on Tadalafil (36/54) reported a duration of action longer than 24 h, 14 patients between 4 and 24 h and four patients a duration equal or less than 4 h.

ANOVA showed a negative impact of cauda equina lesions and lower motor neuron lesion, others variables such as completeness of lesion had no impact.

Home assessments
In the follow-up visits, we reviewed 57 patients on Sildenafil, 12 patients on Vardenafil and 21 patients on Tadalafil. The duration of use ranged from 3 to 20 months (mean of 9.7 ± 3.7 months) (Table 3).

The IIEF global score was significantly improved in all patients. There was a statistically significant improvement of three IIEF domains (erectile function, intercourse satisfaction and overall satisfaction) with

Table 3 Baseline assessments and efficacy outcome at home

	Sildenafil (n = 56)		*Vardenafil* (n = 12)		*Tadalafil* (n = 21)		
	Baseline	*Home*	*Baseline*	*Home*	*Baseline*	*Home*	
IIEF global score	34.3 (4.7)	57.7* (7.7)	34.4 (7.3)	56.2* (4.7)	39.6 (8.9)	56.6* (5.3)	NS
Erectile function IIEF Q. 1–5, 15	14.0 (3.2)	26.8* (3.4)	15.8 (5.0)	28.7* (1.8)	18.6 (5.5)	28.4* (1.7)	NS
Intercourse satisfaction IIEF Q. 6–8	6.5 (2.1)	9.2* (1.7)	4.6 (0.9)	8.6* (1.3)	6.0 (2.0)	8.5* (1.3)	NS
Orgasmic function IIEF Q. 9, 10	2.4 (0.8)	5.0* (2.1)	2.5 (0.9)	3.1 (1.6)	3.0 (2.0)	3.3 (2.2)	S
Sexual desire IIEF Q. 11, 12	9.1 (1.1)	9.1 (1.2)	8.9 (1.0)	9.0 (1.1)	8.8 (1.1)	8.9 (0.9)	NS
Overall satisfaction IIEF Q. 13, 14	2.3 (0.7)	7.8* (1.8)	2.5 (0.9)	6.7* (1.6)	3.2 (1.6)	7.5* (2.1)	NS

Mean (SD)
*Significant difference in each group
NS: nonsignificant; S: significant difference between the three groups

the three PDE5 inhibitors. Patients on Sildenafil showed a significant improvement of orgasmic function, ejaculation (Question 9) from 1.2 ± 0.6 to 2.3 ± 1.3 and orgasm (Question 10) from 1.3 ± 0.5 to 2.7 ± 1.2. The sexual desire remained high in all patients.

Discussion

The clinic trials confirmed that PDE5 inhibitors are effective in treating ED. Good rigidity associated with a duration of erection of more than 25 min was found in more than 72% of SCI patients. These results are in line with other randomized or placebo-controlled studies.[8,10–12,14–16]

The adverse effects of PDE5 inhibitors were mild in 6–15% of the patients. No episode of severe hypotension was experienced, probably because patients prone to blood pressure instability were excluded from this study.[17,18]

Patients presenting with upper motor neuron lesions are good responders to the treatment, whereas patients with a cauda equina lesion and/or lower motor neuron lesions are poor responders. These results indicate that the sparing of the spinal sacral parasympathetic centre (spinal cord segment S2–S4) that mediates reflexogenic erection is the key factor for efficacy. In these cases, PDE5 inhibitors amplify the physiological NO/cGMP mechanism and reinforce the existing mechanical erection.[8,15]

Home-based assessments showed that PDE5 inhibitors significantly improve the sexual life of SCI patients, particularly in the IIEF domains of erectile function, intercourse satisfaction and overall satisfaction for the three drugs. These results are in line with other randomized or placebo-controlled studies.[8,10–12,14,16]

Orgasmic function was low in all three groups of patients on baseline assessments, but ejaculation (Question 9) and orgasm (Question 10) significantly improved on Sildenafil. Ejaculatory dysfunction is frequent in SCI patients, as only about 15% of the patients report ejaculation during sexual intercourse.[5,19] Orgasm feeling is poor in most SCI patients, as reflected by clinical studies using the IIEF questionnaire.[8,11,15] Although the issue of orgasm in SCI men has been rarely addressed, it seems that orgasm is often accompanied by ejaculation,[20] as in normal men. The reason why the improvement of orgasmic function is obtained with Sildenafil only is not clear. We can hypothesize a direct or indirect effect of Sildenafil on genital organs, or an enhanced reflex response of the receptors of the prepuce owing to better tension of the glans with Sildenafil.

With the initial dose of 50 mg, Sildenafil was effective in 55% of the patients, whereas the maximal dose of 20 mg was required in more than 70% of the patients on Tadalafil and Vardenafil. Furthermore, Sildenafil was associated with a higher percentage of rigidity and longer duration of erection than Vardenafil and Tadalafil. Although no statistical analysis could be applied on these data, these results might indicate that Sildenafil is more effective in treating ED.

Two-thirds of our patients on Tadalafil reported a duration of action longer than 24 h. Tadalafil has a half-life of 17.5 h, and has been shown to be efficacious up to 36 h after dosing, which can give more spontaneity, and allow patients to decide when to engage in sexual intercourse with a partner.[12,21] As a consequence, some of our SCI patients take Tadalafil on a regular basis three times/week rather than on-demand. However, care must be taken with patients wearing penile sheaths or tight clothes, as excessive stimulation can cause unwanted mechanical erections. For this reason, we never prescribe Tadalafil as a first treatment.

In our experience, the clinic trials with PDE5 inhibitors are of great importance. The side effects of PDE5 inhibitors can be diagnosed and dealt with and appropriate dose titration can be performed. Proper education is given to the patients, such as restrictions regarding previous food and alcohol consumption or appropriate time administration with regard to the initiation of sexual activity, together with the presence of adequate sexual stimulation.[22] After successful trials, patients are more confident in getting and keeping an erection of good quality. Studies have demonstrated that satisfaction with sexual life is related to an improvement in quality of life.[16,23] The restoration of an erectile function is an important step toward higher

self-esteem and body image of these patients allowing for social reinsertion.

Conclusion

This study confirms the safety and efficacy of PDE5 inhibitors in the treatment of ED of the SCI patients. Sildenafil, Vardenafil and Tadalafil are all effective in improving sexual function in SCI patients, especially in quality of erection and satisfaction with sex life. PDE5 inhibitors are significantly more effective in patients presenting with upper motor neuron lesions and having reflexogenic erections. This oral treatment is preferred by most patients, but is expensive and not reimbursed in France.

Although we did not try to compare the efficacy of each drug, we found some differences. Sildenafil is associated with a significant improvement of orgasmic function, possibly related to a better quality of erection, but with a higher rate of side effects. Tadalafil and Vardenafil need to be started with the higher dosing of 20 mg. Tadalafil has a longer duration of action, which can give more spontaneity.

Clinic trials are important for proper dose titration and appropriate education of the patients.

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