Effects of Sildenafil on Nocturnal Penile Tumescence and Rigidity in Normal Men: Randomized, Placebo-Controlled, Crossover Study

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ABSTRACT: We studied the effects of sildenafil on sleep-related erections in 44 adult healthy men not affected by erectile dysfunction (mean age ± SD: 39.3 ± 10.5 years). No subjects were administered any medication the first night, but all were randomly administered sildenafil 50 mg or placebo the second night and vice versa the third night. Sildenafil and placebo were administered 1 hour before bedtime. The following parameters of *sleep-related erections*, after taking sildenafil or placebo, were analyzed: total number of valid erections, total duration of rigidity more than or equal to 70% of a tightening force of 2.8 N applied by the recording device, total duration of increase in penile circumference more than or equal to 30 mm, maximum rigidity, mean of maximum rigidity, and maximum increase of tumescence. Apart from the maximum increase of tumescence, all the parameters analyzed were significantly higher after sildenafil than after placebo administration during the first 4 hours

of monitoring in all subjects (n = 44) (study 1). All the parameters were significantly higher after sildenafil than after placebo administration during the whole 8 hours of monitoring in 25 of 44 subjects (study 2A) who slept at least 8 hours. Comparing both the first and the second 4 hours in the 25 of 44 subjects who slept at least 8 hours (study 2B), all the parameters were significantly higher after sildenafil than after placebo administration, apart from maximum rigidity and mean of maximum rigidity during the first 4 hours. Our data suggest that sildenafil, administered at bedtime, is efficacious in improving *sleep-related erections* in normal men, indirectly confirming that the nitric oxide pathway is crucial in the physiology of erections during sleep. The effect of sildenafil is prolonged up to 8–9 hours after its administration.

Key words: Sleep-related erections, healthy men.

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Cyclic guanosine monophosphate (cGMP), the second messenger in the nitric oxide pathway, acts on penile smooth muscle cells by inducing relaxation. Sildenafil is an oral selective inhibitor of type 5 cGMP-specific phosphodiesterase enzyme (PDE-5) that is the predominant isozyme in the corpus cavernosum that degradates cGMP. The sildenafil-dependent PDE-5 inhibition results in an increase of cGMP together with a consequent decrease of intracellular Ca^{++}, finally resulting in a penile smooth muscle relaxation and vasodilatation (Rajfer et al, 1992; Boolell et al, 1996a; Goldstein et al, 1998; Lue, 2000).

Sildenafil is efficacious and safe in men affected by erectile dysfunction (Boolell et al, 1996b; Goldstein et al, 1998; Montorsi et al, 1999; Rendell et al, 1999; Hermann et al, 2000; Lue, 2000), while little is known about the effects of sildenafil in normal men. Recently, it has been suggested that a possible role for sildenafil is in reducing

the postejaculatory refractory time in the presence of a continuous erotic stimulus in men not suffering from erectile dysfunction (Aversa et al, 2000).

Until now, the efficacy of sildenafil on erectile function has been assessed by self-filled questionnaires concerning sexual activity or visual erotic stimulation (Boolell et al, 1996b; Goldstein et al, 1998; Montorsi et al, 1999; Rendell et al, 1999) or by visual erotic stimulation and simultaneous penile rigidity monitoring (Boolell et al, 1996b). These kinds of studies provide results concerning *psychogenic and/or reflexive erections* (erections that occur during waking under the effects of psychogenic or sexual stimuli), which are dependent at least in part on the psychological pattern of the subject.

Sleep-related erections represent a valid clinical model useful to investigate the effects of sildenafil on penile physiology for 2 main reasons. First, the continuous monitoring of *sleep-related erections* by means of a device, provides qualitative and quantitative parameters of penile erections (Bradley, 1987; Kessler, 1988). Second, nocturnal erections are poorly or not affected by external factors (eg, embarrassment, state anxiety), which can interfere with penile erections when studied on awake subjects (Karacan, 1980; Bancroft, 1989; Granata et al, 1995).
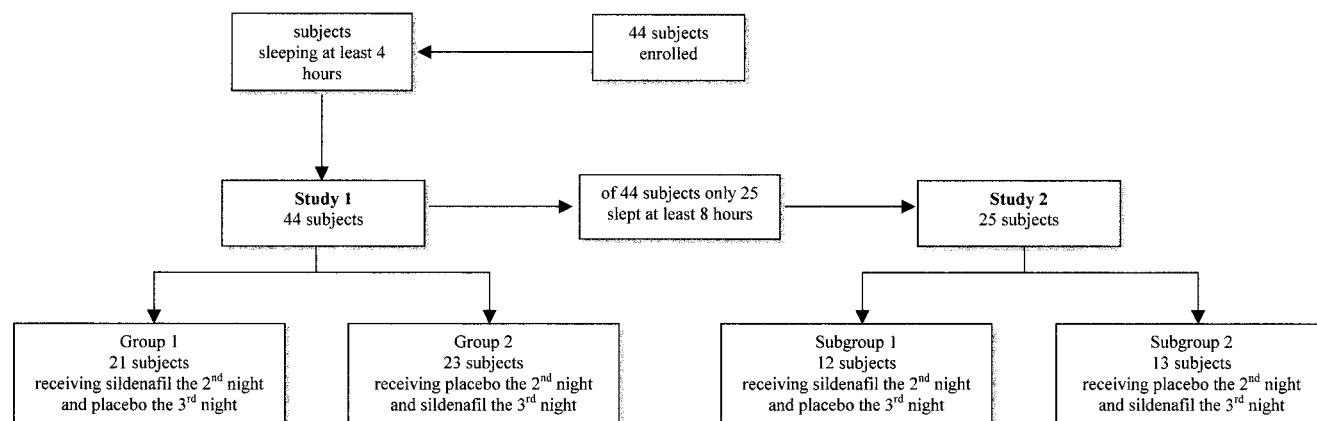
Figure 1. Study design.

Therefore monitoring *sleep-related erections* constitutes a useful tool to evaluate the pure effects of sildenafil per se on erectile function.

In order to evaluate the effects of sildenafil on *sleep-related erections,* we studied healthy men, because nocturnal erections are presumably unaffected in these subjects, as opposed to men affected by erectile dysfunction.

Subjects and Methods

Subjects

Forty-four healthy male volunteers (mean age ± SD: 39.3 ± 10.5 years) were enrolled. All the subjects reported their sexual history and had a physical examination, and all completed the 15-question International Index of Erectile Function questionnaire (Rosen et al, 1997) in order to enroll in the study; only subjects without sexual disturbances were eligible. Depression and trait anxiety were excluded by self-filled questionnaires (Beck et al, 1961; Spielberger et al, 1970). Testosterone and prolactin were assayed to exclude hypogonadism and hyperprolactinemia.

Other inclusion criteria were well-being and no complaint of erectile dysfunction or sleep disturbances. None of the subjects were on any medication during the entire protocol period, and each gave informed consent to the study.

The subjects performed nocturnal penile tumescence and rigidity monitoring (NPTRM) for 3 consecutive nights. Sildenafil or placebo was administered on the second or the third night.

Study Design

The study design was a randomized, placebo-controlled, crossover study as summarized in Figure 1.

Study 1—Of the 44 subjects enrolled, 21 were randomized to group 1, receiving a 50-mg sildenafil tablet the second night, followed by the administration of placebo the third night. Twenty-three subjects were randomized to group 2, receiving placebo the second night, followed by the administration of a 50-mg sildenafil tablet the third night (Figure 1).

All subjects underwent NPTRM during each night for at least 4 hours.

Study 2—Study 2 was performed on a subgroup of 25 subjects (12 from group 1 [subgroup 1] and 13 from group 2 [subgroup 2]) (mean age ± SD: 39.6 ± 13.4 years), which included all the men whose NPTRM lasted at least 8 hours. The aim of study 2 was to evaluate the effects of both sildenafil and placebo on a longer period of sleep than study 1 (Figure 1).

Treatment

An intermediate dosage of sildenafil (50-mg tablet) was used, since the subjects were not affected by erectile dysfunction, and the effects of the drug were likely not counteracted by psychological interference, as *sleep-related erections* are poorly or not at all influenced by external factors (eg, embarrassment, state anxiety) (Bancroft, 1989; Granata et al, 1995). Maximal plasma concentration of sildenafil occurs 1 hour after oral administration, having a mean terminal half-life of about 4 hours (Boolell et al, 1996a), and the effects of sildenafil last up to 4–5 hours from the administration (Eardley et al, 1999). Thus, all the subjects were administered with both sildenafil and placebo 1 hour before starting the night monitoring of penile erections and at least 2 hours after their last meal.

Methods

Each subject underwent NPTRM at home and during 3 consecutive nights by RigiScan (Dacomed Corp, Minneapolis, Minn) (Munoz et al, 1993). The first night was regarded as an adaptation night; the results shown are from the second and third night only. A single RigiScan was used in order to avoid unequal measurements from different devices (Munoz et al, 1993). Only the data recorded by the base loop of the RigiScan are reported. The subjects went to bed at their usual time.

The NPTRM parameters that we analyzed are the following:

1) *Total number of valid erections,* defined as an increase in circumference (at the base of the penis) of at least 30 mm from the baseline and with a rigidity of at least 60%, both circumference increase and rigidity persisting for at least 5 minutes. The baseline for measurement of circumference in-

crease was the minimum circumference, which lasted at least 5 minutes (Granata et al, 1997).

2) Total duration of penile rigidity more than or equal to 70% as the sum of the penile rigidity more than or equal to 70% evaluated in each recorded erection and in a single monitoring.

3) Total duration of increase in penile circumference more than or equal to 30 mm as the sum of the penile tumescence more than or equal to 30 mm evaluated in each recorded erection and in a single monitoring.

4) Maximum penile rigidity (%) persisting for at least 3 minutes in a single monitoring.

5) Mean of maximum rigidity as a mean of the maximum rigidity evaluated in each recorded erection and in a single monitoring.

6) Maximum increase in penile circumference persisting for at least 3 minutes and in a single monitoring.

Statistical Analysis

Data from the NPTRM were analyzed by means of a Student's t test for paired data. The comparisons were considered significant when $P < .05$.

Study 1

The NPTRM parameters obtained from the first 4 hours of continuous penile function monitoring of the 44 healthy male volunteers were analyzed. The data from the sildenafil group were compared with those from the placebo group (Student's t test for paired data).

Study 2A and B

The NPTRM parameters obtained from the subgroup of 25 men who reached 8 hours of continuous monitoring were analyzed. The data from the sildenafil subgroup were compared with those from the placebo subgroup.

Study 2A—The data from all 8 hours of continuous penile monitoring were analyzed by comparing the outcomes from the sildenafil subgroup with those from the placebo subgroup (Student's t test for paired data).

Study 2B—The data obtained from 8 hours of monitoring were divided in a time-dependent manner. The outcomes from the first 4 hours (hours 0–4) of the test from the sildenafil subgroup were compared with those from the placebo subgroup. In the same way, the outcomes from the second 4 hours (hours 4–8) of the test from the sildenafil subgroup were compared with those from the placebo subgroup.

Results

None of the 44 subjects reported side effects after taking placebo or sildenafil.

Study 1

The number of valid erections ($P < .05$), total duration of rigidity more than or equal to 70% ($P < .0001$) (Figure 2), total duration of increase of penile tumescence more
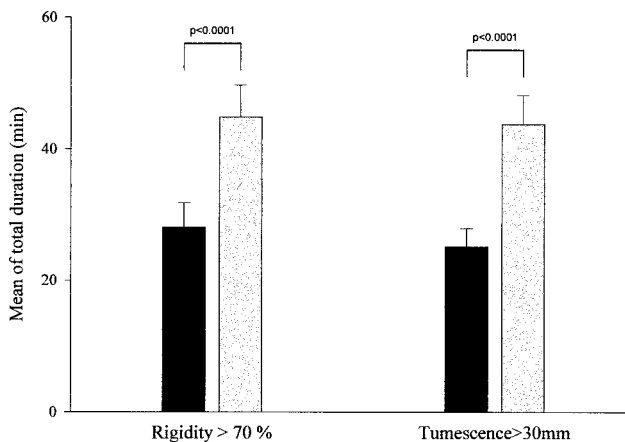
Figure 2. Mean of total duration of rigidity more than or equal to 70% and increase of tumescence more than or equal to 30 mm after placebo (black) or sildenafil (gray) administration (study 1): data are from 44 healthy male subjects during the first 4 hours of nocturnal penile tumescence and rigidity monitoring.

than or equal to 30 mm ($P < .0001$) (Figure 2), maximum rigidity ($P < .05$), and mean of maximum rigidity ($P < .01$) were significantly higher after sildenafil administration than after placebo (Table).

The maximum increase of tumescence did not change when comparing placebo data with sildenafil data (Table).

Study 2A and B

Study 2A—The number of valid erections ($P < .0001$), total duration of rigidity more than or equal to 70% ($P < .0001$) (Figure 3), total duration of increase of penile tumescence more than or equal to 30 mm ($P < .0001$) (Figure 3), maximum rigidity ($P < .05$), mean of maximum rigidity ($P < .05$), and maximum increase of tumescence ($P < .05$) were significantly higher after sildenafil than after placebo administration (Table).

Study 2B—Focusing on the first 4 hours (hours 0–4) of monitoring, the number of valid erections ($P < .01$), total duration of rigidity more than or equal to 70% ($P < .01$) (Figure 4), total duration of increase of penile tumescence more than or equal to 30 mm ($P < .0001$) (Figure 4), and maximum increase of tumescence ($P < .05$) were significantly higher after sildenafil than after placebo administration (Table). The maximum rigidity and the mean of maximum rigidity were not significantly different, even though a trend toward higher values after sildenafil was present.

Focusing on the second 4 hours (hours 4–8) of monitoring, the number of valid erections ($P < .0001$), total duration of rigidity more than or equal to 70% ($P < .0001$) (Figure 4), total duration of increase of penile tumescence more than or equal to 30 mm ($P < .0001$) (Figure 4), maximum rigidity ($P < .01$), mean of maximum rigidity ($P < .05$), and maximum increase of tumescence

Table. Nocturnal erectile parameters after sildenafil or placebo administration on both study 1 and study 2; study 1 included all subjects whose nocturnal penile tumescence and rigidity monitoring lasted at least 4 hours, and study 2 involved a subgroup of 25 whose nocturnal erectile monitoring lasted at least 8 hours (values are means [SE])

| | Study 1 | | | Study 2A | | | Study 2B | | | | | |
| | | | | | | | First 4-h Monitoring | | | Second 4-h Monitoring | | |
	Placebo (n = 44)	Sildenafil (n = 44)	P* Value	Placebo (n = 25)	Sildenafil (n = 25)	P* Value	Placebo (n = 25)	Sildenafil (n = 25)	P* Value	Placebo (n = 25)	Sildenafil (n = 25)	P* Value
No. of valid erections	1.73 (0.13)	2.09 (0.15)	.025	3.12 (0.26)	4.44 (0.29)	.000	1.56 (0.13)	2.12 (0.18)	.008	1.6 (0.19)	2.44 (0.18)	.000
Total duration of rigidity ≥70% (minutes)	28.09 (3.71)	44.81 (4.90)	.000	70.10 (8.02)	117.98 (10.82)	.000	31.96 (5.26)	45.11 (6.68)	.005	37.73 (5.47)	72.85 (6.42)	.000
Total duration of increase of tumescence ≥30 mm (minutes)	25.09 (2.79)	43.71 (4.40)	.000	51.67 (6.76)	107.50 (11.20)	.000	23.17 (3.76)	42.67 (5.64)	.000	28.78 (4.32)	66.52 (6.88)	.000
Maximum rigidity (%)	80.57 (3.34)	87.04 (2.39)	.017	89.82 (1.92)	93.34 (0.37)	.016	83.54 (4.03)	89.19 (1.68)	.140	86.9 (2.4)	92.82 (1.37)	.007
Mean of maximum rigidity (%)	73.07 (3.15)	80.48 (2.35)	.004	80.86 (2.30)	85.42 (1.79)	.010	76.50 (3.99)	83.19 (1.89)	.08	82.23 (2.62)	87.80 (2.00)	.026
Maximum increase of tumescence (mm)	38.73 (1.94)	40.47 (1.56)	.125	40.24 (1.55)	43.48 (1.61)	.010	37.76 (2.08)	40.67 (1.71)	.038	38.36 (1.72)	43.28 (1.60)	.002

* P value derived from Student's *t* test for paired data. The comparisons were considered significant when P < .05.
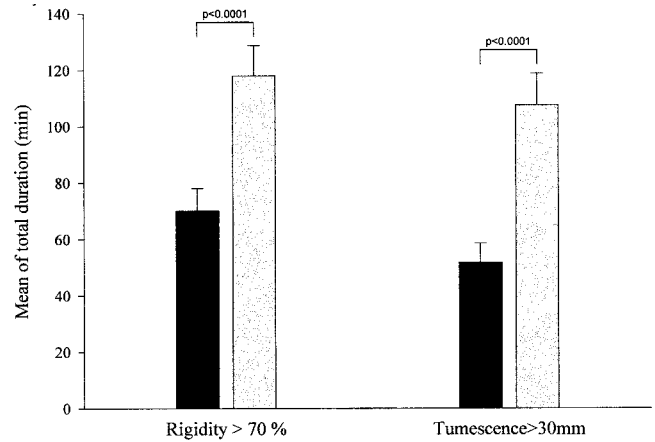

Figure 3. Mean of total duration of rigidity more than or equal to 70% and increase of tumescence more than or equal to 30 mm after placebo (black) or sildenafil (gray) administration (study 2A): data are from 25 of the 44 subjects during 8 hours of nocturnal penile tumescence and rigidity monitoring.

(P < .01) were significantly higher after sildenafil than after placebo administration (Table).

It is noteworthy that a comparison of NPTRM parameters was performed between the subjects who were administered sildenafil on the second night and the subjects who were administered sildenafil on the third night. The same analysis was performed for placebo. No significant differences were observed with these analyses, suggesting that our results are independent from the day of administration of the drug during the protocol.

Discussion

This study demonstrates that a 50-mg sildenafil tablet at bedtime is effective in improving nocturnal erections in men whose penile function is characterized by both full *sleep-related erections* (spontaneous erections) and full erections during sexual intercourse (erections induced by erotic stimulation and influenced by psychological factors). In fact, sildenafil significantly ameliorates both penile rigidity and tumescence during sleep in the healthy men we have studied.

A similar result on nocturnal erections was previously obtained from patients who had erectile dysfunction, but with a higher dosage of sildenafil (Montorsi et al, 2000). In the present study, a dosage of sildenafil lower than that used in the Montorsi study (Montorsi et al, 2000) improved *sleep-related erections* in normal men; the efficacy of a lower dosage is probably due to the absence of any impairment in the erectile function in these healthy men.

Our results on *sleep-related erections* are in agreement with anecdotal data and with the poor data available in
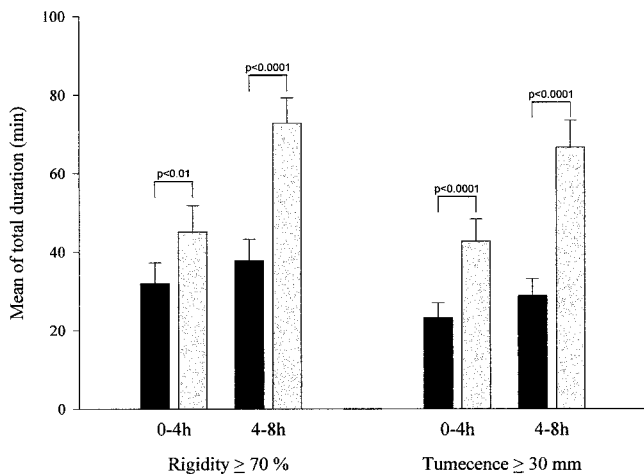
Figure 4. Mean of total duration of rigidity more than or equal to 70% and increase of tumescence more than or equal to 30 mm after placebo (black) or sildenafil (gray) administration (study 2B): data are from 25 of the 44 subjects during the first 4 (hours 0–4) and the second 4 hours (hours 4–8) of nocturnal penile tumescence and rigidity monitoring.

the literature concerning the effects of sildenafil on penile erections in normal men when awake. A positive role of sildenafil in normal men was previously suggested by studying *psychogenic erections* in normal male volunteers (Aversa et al, 2000); furthermore, young English men not complaining of erectile dysfunction noted better sexual function by using sildenafil as a recreational drug (Aldridge and Measham, 1999).

As expected, our data indirectly show that the nitric oxide pathway is crucial for both *sleep-related erections* and erections occurring during waking (*psychogenic* and *reflexive erections*) (Giuliano et al, 1995). In fact, even normal sleep-related erections are improved by sildenafil, and this drug undoubtedly acts by the nitric oxide pathway.

Study 2B shows that sildenafil is efficacious in improving erectile parameters not only during the first 4 hours of the test but, surprisingly, also during the second 4 hours. This means that sildenafil is efficacious even up to 8 hours from the beginning of the NPTRM and up to 9 hours from taking the medication. A previous report on penile response during visual erotic stimulation suggests that sildenafil reaches its highest efficacy 2–3 hours from administration, even though a small but lower efficacy is maintained up to 4–5 hours (Eardley et al, 1999). However, some subjects involved in the Eardley et al (1999) study and in other trials (Boolell et al, 1996b) claimed that the efficacy of sildenafil was still present the morning after taking the medication, suggesting a more prolonged action of the drug when it is taken before sleep. The data from *sleep-related erections* and from penile response to visual erotic stimulation (*psychogenic erections*) seem to be contradictory (Eardley et al, 1999), but it needs to be emphasized that *sleep-related erections,* as opposed to

psychogenic erections, are poorly or not affected by external factors (eg, embarrassment, state anxiety) (Karacan, 1980; Bancroft, 1989; Granata et al, 1995); therefore, these 2 sorts of erections are not completely comparable.

Several hypotheses may support the finding of better erections during the second 4 hours of our study after sildenafil is taken. As a first hypothesis, sildenafil could have a longer half-life in cavernous tissue than in the systemic blood (Boolell et al, 1996a). Second, sildenafil acts on PDE-5 by inducing a reversible inhibition of its activity, but it is not known how long PDE-5 inhibition lasts after sildenafil concentration in systemic blood is decreased because of the metabolism of sildenafil itself. However, a more reliable hypothesis is probably based on the oxygen tension in the penile tissue. Sildenafil administration improves the duration of the erections during the first 4 hours of monitoring, possibly leading to an increased oxygen tension in the penile tissue, which could facilitate both the occurrence and the quality of the following erectile episodes. In the penile tissue, nitric oxide production has been suggested to be dependent on oxygen tension: a decrease in oxygen tension in the flaccid state is related to poor activity of nitric oxide synthase and to lower levels of nitric oxide, while an increase in oxygen tension promotes both nitric oxide synthase activity and nitric oxide production (Kim et al, 1993). Therefore better previous erectile episodes may improve the following ones by facilitating the action of the initiating nervous stimuli, which affect a penile microenvironment more predisposed to start the nitric oxide cascade.

In this view, sildenafil has been regarded as an enhancer of penile tissue oxygenation, suggesting a possible role of this drug in preventing the damage of corpora cavernosa induced by hypoxia, which is thought to be involved in the pathogenesis of erectile dysfunction (Sattar et al, 1995; Moreland, 1998). Sildenafil administration at bedtime has been suggested as a treatment to prevent penile damage due to hypoxia and to maintain or to ameliorate erectile function (Montorsi et al, 2000). According to our results, the suggestions by Montorsi et al (2000) that sildenafil could be a preventative treatment of penile damage could even be applied to men at risk of penile damage due to hypoxia but with both sleep-related erections and erections during waking still normal. However, in order to confirm sildenafil's long-term action, to clarify the mechanism of this time action, and to confirm and clarify the role of hypoxia in penile damage, further efforts are needed.

In conclusion, this study shows that sildenafil, administered as a single oral dose before bedtime, is effective in improving the nocturnal penile erections in men not affected by erectile dysfunction. The effect of sildenafil on *sleep-related erections* lasts up to 8–9 hours after its

administration, suggesting a more prolonged action than when administered to awake subjects.

Acknowledgment

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