

Duration of Action of Sildenafil Citrate in Men with Erectile Dysfunction

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ABSTRACT

Introduction. Viagra[®] (sildenafil citrate) has a rapid onset of action for the treatment of erectile dysfunction (ED). However, its duration of action has not been thoroughly investigated. Practical knowledge of the time window available for sexual intercourse would be valuable for couples planning sexual activity.

Aim. We investigated the duration of action of sildenafil in men with ED.

Methods. This was a double-blind, randomized, placebo-controlled, four-way crossover study of 16 men, mean age of 55 years (range, 36–68 years) with ED of no known organic cause. Participants received oral sildenafil (100 mg) or placebo 1, 8, or 12 hours before visual sexual stimulation (VSS). Measurements included the duration of erections of $\geq 60\%$ rigidity, assessed by penile plethysmography (RigiScan[®]), and the proportion of sildenafil responders, defined as patients with erections of $\geq 60\%$ rigidity for ≥ 4 minutes and $\geq 50\%$ improvement over erections achieved in their placebo arm. Self-assessed duration of grade 3 (hard enough for penetration) or grade 4 (fully hard) erections was also recorded.

Results. At 1, 8, and 12 hours after dosing with sildenafil, the mean duration of erections with $\geq 60\%$ rigidity was 26, 11, and 8 minutes, respectively, compared with only 3 minutes after placebo dosing ($P < 0.05$). However, the mean duration of self-assessed erections was 33, 23, and 16 minutes, respectively, compared with 7 minutes after placebo dosing ($P < 0.05$), and was greater than that assessed by RigiScan. Of the 69% sildenafil responders at 1 hour, 82% responded at 8 hours and 45% responded at 12 hours after sildenafil administration.

Conclusion. Sildenafil improved objective and self-assessed erectile function in men with ED, and the duration of action of sildenafil was longer than that previously reported. These data suggest that sildenafil may be effective in a significant proportion of men with ED up to 12 hours after being taken.

Key Words. Erectile dysfunction; Sildenafil; Placebo-Controlled; Randomized; Duration of Action

Introduction

More than 30 million men are estimated to have erectile dysfunction (ED) in the U.S. [1]. Worldwide ED is estimated to affect greater than 150 million men, which is expected to exceed 300 million men by the year 2025 [2]. Moreover, recent research suggests that ED may be an early indicator of systemic vascular disease [3]. Sildenafil citrate, the first-in-class phosphodiesterase type 5 (PDE5) inhibitor for the treatment of ED [4], has

an excellent safety and efficacy record. Clinical studies show that sildenafil successfully treats ED in men with comorbidities such as hypertension [5], diabetes [6], and depression [7], and suggest that successful treatment of ED can improve overall quality of life [8]. However, the duration of action of sildenafil in men with ED has not been thoroughly investigated.

Previous studies have shown that sildenafil can help men achieve an erection adequate for penetration in as early as 12 minutes and within

30 minutes of dosing for most men [9,10]. In a cohort of 17 men, the median onset of action of a 50-mg dose of sildenafil was 27 minutes, and the plasma half-life was 3–5 hours [9]. This is a suitable time frame for most couple's sexual activity [11]. Interestingly, 81% of men and 89% of women believe that sexual intercourse more than once in a 24-hour period is of little importance [11]. Considering the rapid onset of action of sildenafil, practical knowledge of the time window of opportunity available for sexual intercourse would be valuable for couples planning sexual activity. Therefore, we studied the duration of action of a single dose of sildenafil in men with ED of no known organic cause.

The penile plethysmography (RigiScan, Dacomed Corporation, Minneapolis, MN) technique is a well-established method for measuring penile erectile activity [12,13]. This technique is used with visual sexual stimulation (VSS) to assess the efficacy of treatment in ED patients [4]. In this study we assessed the efficacy of sildenafil at 8 and 12 hours post-dose relative to that observed at 1 hour post-dose. This allows a comparison of the later time points with a period where good erectile activity is observed [9].

Methods

Study Design

Men with diagnosed ED of no known organic cause were randomized into four sequence groups (I–IV) in a four-way crossover, double-blind, placebo-controlled trial (Table 1). Each subject underwent a screening visit, four-study periods and a follow-up visit. Each study period was separated by a minimum of 7 days and involved a 14-hour inpatient stay. During each study period, subjects received oral doses of blinded medication at three time points; 12, 8 and 1 hour before the start of VSS. During three of the study periods, subjects received a 100-mg sildenafil tablet at one time point and placebo tablets at the remaining two time points. During the control study period, subjects received placebo tablets at all three time points. This ensured full blinding of the study.

Subjects

Sildenafil-naïve men were eligible to participate in this study if they were between the ages of 18 and 70 years and had been diagnosed with ED of no known organic cause for ≥ 6 months' duration. ED was defined as the persistent inability to attain

Table 1 Sequence groups and test periods*

Sequence	Period 1	Period 2	Period 3	Period 4
I	A	B	C	D
II	C	A	D	B
III	B	D	A	C
IV	D	C	B	A

* Subjects were randomized into sequence groups (I–IV) and sildenafil or placebo was administered in test periods A–D at the following times before visual sexual stimulation: A, 12 hours; B, 8 hours; C, 1 hour; D, placebo at each time point.

and/or maintain penile erection sufficient for satisfactory sexual performance. Men were excluded if they had not experienced at least one erection of sufficient rigidity for penetrative sexual intercourse (including morning erections) in the previous 4 weeks, or failed to give a positive response to intracavernosal prostaglandin (dose not exceeding 20 μg), or papaverine (dose not exceeding 40 mg), at screening. The inclusion of men who failed to achieve an erection would have been inappropriate for a study of the duration of action of sildenafil. Men were also excluded if they had a history of diabetes; untreated hypogonadism; significant arterial, renal, or hepatic disease; or had used antidepressants, tranquilizers, nitrates, intracavernosal injections, or any other treatment for ED in the 2 weeks before, or at any time during, the study. Subjects provided informed written consent, an Ethics Review Committee approved the study, and the study was performed in accordance with the Helsinki Declaration.

Efficacy Assessments

The primary efficacy outcome was duration of erections with $\geq 60\%$ rigidity at the base of the penis, as measured by penile plethysmography (RigiScan). RigiScan data were collected starting 15 minutes before VSS and continuing for 1 hour of VSS at each study visit. The data were analysed for the number, quality, and duration of erections during VSS.

The secondary efficacy outcomes were patient analysis of penile erection and percentage of sildenafil responders. Following VSS, subjects were asked to give a subjective self-assessment of penile erection, if achieved. Self-assessment was based on a scale from 1 to 4 (grade 1, increase in size but not hard; grade 2, hard but not hard enough for penetration; grade 3, hard enough for penetration, but not completely hard; grade 4, completely hard). The duration of self-assessed grade 1 to 4 erections was recorded.

In addition, the percentage of responders to sildenafil at each time point was determined. A responder was defined as a subject who had a minimum of 4 minutes of erections of $\geq 60\%$ rigidity on penile plethysmography during VSS in the active treatment period and had $\geq 50\%$ improvement in the duration of these erections in the active treatment period compared with the placebo treatment period.

Statistical Analysis

Differences between the control and treatment groups were determined using repeated-measures ANOVA, and the sample size of 16 was sufficient to detect a fourfold increase in duration of erections of $\geq 60\%$ rigidity relative to placebo with a probability of 0.8 at the 5% level of significance.

Safety Assessment

All reported and observed adverse events (AEs) and vital characteristics were recorded for the duration of the study and for 2 weeks following the last dose of study medication taken.

Results

Demographics

Seventeen participants were enrolled, but one subject was excluded from the efficacy analysis because he received intracavernosal injection therapy during the study. All participants were included in the safety analysis, and 16 participants were included in the intent-to-treat group. The mean age of subjects was 55 years (range, 35–68 years), the mean weight was 83 ± 10 kg, and 16 of 17 were white.

Efficacy

Compared with placebo, sildenafil was effective in increasing the duration of erections at all time points tested. The duration of erections of $\geq 60\%$ rigidity assessed by RigiScan after administration of sildenafil 1, 8, and 12 hours before VSS was 26, 11, and 8 minutes, respectively. By comparison, the duration of erections of $\geq 60\%$ rigidity after administration of placebo was only 3.4 minutes (Figure 1). The duration of self-assessed grade 3 or grade 4 erections when sildenafil was given 1, 8, and 12 hours before VSS was 33, 23, and 16 minutes, respectively. By comparison, the duration of self-assessed grade 3 or grade 4 erections achieved after administration of placebo was only 7 minutes (Figure 2).

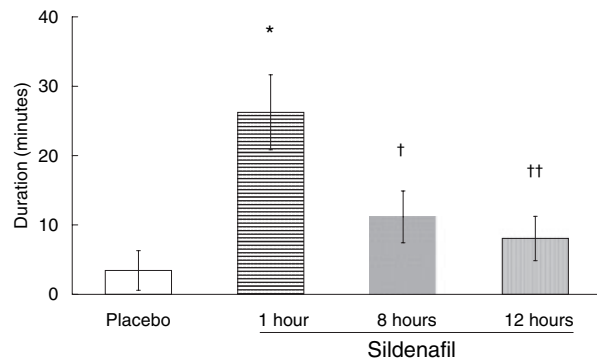


Figure 1 Mean duration of erections after administration of sildenafil assessed by RigiScan. Male participants were administered placebo or sildenafil 1, 8, and 12 hours before visual sexual stimulation. Objective determination of erection hardness was determined by penile plethysmography using RigiScan. Sildenafil increased the duration of erections of $\geq 60\%$ rigidity, lasting ≥ 4 minutes at all time points tested. Data represent mean \pm SE, * $P \leq 0.0001$; † $P \leq 0.0089$; †† $P \leq 0.053$.

Administration of sildenafil before VSS was associated with a high number of responders. The percentage of responders following treatment with sildenafil 1, 8, and 12 hours before VSS was 69%, 60%, and 31%, respectively (Figure 3). Additionally, of the men who responded to VSS 1 hour after sildenafil administration, 82% had a positive response to VSS after 8 hours, and 45% had a positive response 12 hours after sildenafil administration (Table 2).

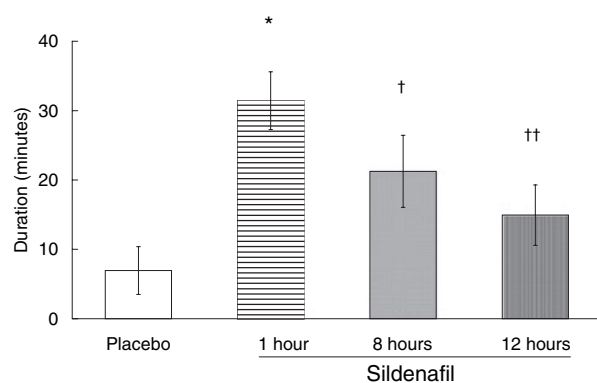


Figure 2 Self-assessed mean duration of erections after administration of sildenafil. Male participants were administered placebo or sildenafil 1, 8, and 12 hours before visual sexual stimulation. Subjects determined the hardness of their erections by self-assessment. Sildenafil increased the mean duration of self-assessed erections of grade 3 (hard enough for penetration) or grade 4 (fully hard) at all time points tested. Data are mean \pm SE, * $P \leq 0.0001$; † $P \leq 0.0004$; †† $P \leq 0.0322$.

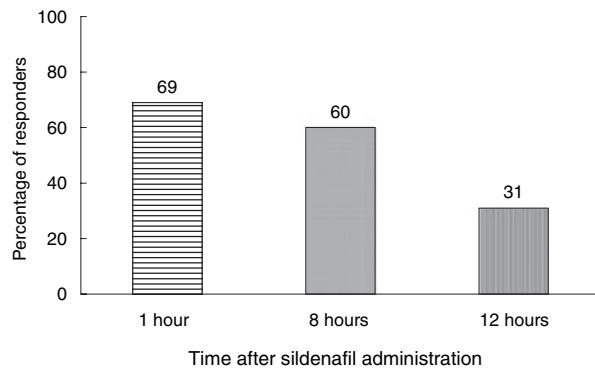


Figure 3 Percentage of sildenafil responders to visual sexual stimulation (VSS). The proportion of sildenafil responders at 1, 8, and 12 hours post-dose was 69%, 60%, and 31%, respectively. Of those who were classified as a responder at 1 hour, 82% responded to sildenafil at 8 hours post-dose and 45% responded at 12 hours post-dose. A responder was defined as a subject who had ≥ 4 minutes of erections of $\geq 60\%$ rigidity during VSS in the active treatment period, and had $\geq 50\%$ improvement in duration of these erections compared with erections during the placebo treatment period.

Safety

Consistent with previous studies, sildenafil was well tolerated (Table 3); the most common AEs reported were headache and facial flushing, which were transient and mild-to-moderate in severity.

Discussion

Sildenafil was well tolerated and efficacious at increasing the duration of erections in men with ED of no known organic cause when administered 1, 8, and 12 hours before sexual stimulation. Interestingly, the duration of self-assessed grade 3 and grade 4 erections was longer than the duration of erections assessed by RigiScan. This suggests that men may perceive a greater benefit than that which is measured objectively using the RigiScan technique. These data further suggest that men

Table 2 Proportion of sildenafil responders* to visual sexual stimulation after administration of sildenafil or placebo

Time after dosing	% responders	% of 1 hour responders
1 hour	73	100
8 hours	60	82
12 hours	33	45

* Patients with erections of ≥ 4 minutes duration with $\geq 60\%$ rigidity and $\geq 50\%$ increase in duration compared with placebo.

Table 3 Adverse study events

	Placebo	Sildenafil		
		1 hour pre-VSS	8 hours pre-VSS	12 hours pre-VSS
Headache	0	1	6	5
Vasodilatation (flushing)	0	2	4	3
Diarrhea	0	0	1	0
Dry mouth	0	0	1	0
Gastrointestinal disorder	1	0	1	1
Respiratory tract infection	0	0	1	0
Chromatopsia	0	0	1	1

VSS, visual sexual stimulation.

with ED may have a therapeutic window up to 12 hours after taking sildenafil for engaging in sexual activity; this is significantly greater than the traditionally recommended 4-hour therapeutic window. Initially, 4 hours was determined to be the effective time for engaging in sexual activity based on the plasma half-life [14]. However, recent empirical testing demonstrates that 75% of men report grade 3 or 4 erections 2 hours after taking sildenafil [9], and that the activity of sildenafil can last as long as 12 hours after administration [15]. In this study, we have shown that of those classified as responders at 1 hour post-dose, 82% responded to sildenafil at 8 hours post-dose and 45% responded at 12 hours after drug administration.

A recent study of the sexual habits of men and women shows that less than 1 hour passes between a man's or woman's initial thoughts of sexual activity and initiation of sexual activity [11], and that 81% of men and 89% of women believe that sexual intercourse more than once in a 24-hour period is of little importance [11]. Taken together, these studies suggest that sildenafil may provide the flexibility that is likely to meet the needs of most couples. In fact, long-term follow-up studies of clinical trials investigating the safety and efficacy of PDE inhibitors for the treatment of ED show that $>95\%$ of men treated with sildenafil are satisfied with their treatment [16,17].

Newer PDE inhibitors have recently joined the therapy options for the treatment of ED. Vardenafil and tadalafil have identical mechanisms of action as sildenafil and the onset of action of vardenafil is similar to sildenafil; tadalafil requires up to an hour [18,19]. The half-life of vardenafil is similar to that of sildenafil, at about 4 hours, but limited safety data exist [20]. The half-life of tadalafil is roughly 17 hours, and consequently has

a longer efficacy window, although less is known about its safety profile than sildenafil [21]. In addition, sildenafil is greater than 10-fold more selective for PDE5 than for any other PDE. Vardenafil and tadalafil, on the other hand, are only fourfold and fivefold more selective for PDE5 than for PDE6 (rods and cones of the eye) and PDE11 (testis and sperm), respectively [18,19]. Extended systemic exposure to PDE5 inhibitors, or inhibition of other PDEs, could present clinical problems. For example, the use of nitrates is contraindicated for 24 hours after either sildenafil [22] or vardenafil [23], and for 48 hours after tadalafil [24]. Extensive clinical trials and real world experience suggest that sildenafil is well tolerated, and it is expected that the PDE5 inhibitors as a class will maintain this excellent safety profile. The current study shows that sildenafil increases the duration of satisfactory erections for up to 12 hours, a period of time most couples believe is sufficient for sexual activity.

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