MINIMAL TIME TO SUCCESSFUL INTERCOURSE AFTER SILDENAFIL CITRATE: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Objectives. To determine the minimal time to successful intercourse after taking sildenafil citrate for erectile dysfunction (ED).

Methods. Male patients with ED (mean age 60 years; mean ED duration 7.0 years) who were successfully treated with sildenafil (100 mg) for 2 months or longer were randomized to sildenafil (n = 115) or placebo (n = 113) for 4 weeks of double-blind treatment. Using a stopwatch, patients recorded the time needed to obtain an erection hard enough for sexual intercourse after taking the study drug at least 2 hours after eating.

Results. Within 14 and 20 minutes of sildenafil dosing, 35% and 51% of sildenafil-treated patients, respectively, versus 22% and 30% of placebo-treated patients, respectively, had an erection that led to successful intercourse (P < 0.05 for both). The median time to erection leading to successful intercourse after sildenafil dosing was 36 minutes compared with 141 minutes for placebo.

Conclusions. In this study, slightly more than one half of a population of prior sildenafil responders achieved an erection that led to successful sexual intercourse within 20 minutes of sildenafil administration, suggesting that the onset of action of sildenafil can be less than 30 minutes in men with ED. UROLOGY 62: 400–403, 2003. © 2003 Elsevier Inc.

More than 20 million patients have been treated with sildenafil citrate as therapy for erectile dysfunction (ED). Sildenafil is rapidly absorbed, with maximal plasma concentrations reached within 30 to 120 minutes of oral dosing in the fasted state. Although some patients reported times to erection of less than 30 minutes, most studies evaluating the efficacy of sildenafil as therapy for ED directed patients to take sildenafil approximately 1 hour before sexual activity, and hence, it is commonly thought that sildenafil takes at least 1 hour before it begins working. The present study was conducted to determine more precisely the minimal time to the onset of an erection after administration of sildenafil in men with ED.

MATERIAL AND METHODS

PATIENTS

The patients were men aged 18 years or older with clinically documented ED of at least 6 months' duration who had previously responded successfully to sildenafil and who had been treated for a minimum of 2 months with a stable 100-mg sildenafil dose. Patients were required to be in an established single-partner relationship and to discontinue all medications for ED, including their prescription for sildenafil. Patients who had been prescribed, were taking, or were likely to be treated with nitrates or nitric oxide donors and those with hypotension (blood pressure less than 90/50 mm Hg), hypertension (blood pressure greater than 170/110 mm Hg), or significant cardiovascular disease (eg, cardiac failure, myocardial infarction, unstable angina, stroke, or symptomatic or clinically significant cardiac abnormalities in the past 3 months) were excluded. All patients gave written informed consent, and the institutional review board at each study center approved the study protocol.

STUDY DESIGN

After a 2-week treatment-free baseline period, patients were randomized to 4 weeks of double-blind treatment with...
100-mg sildenafil or matching placebo. Patients were given detailed instructions on dosing, stopwatch use, and filling out the sexual activity event log. Patients were to take the study medication as needed for sexual activity, but not more than once daily. The study medication was taken with a glass of water on an empty stomach (at least 2 hours after eating), and no alcoholic beverages were to be consumed for at least 2 hours before taking the study medication. Patients were asked to record the time study medication was taken immediately in their sexual activity event log, to start the stopwatch, and then to begin sexual stimulation. The patient stopped the stopwatch when an erection that was considered hard enough for sexual intercourse was achieved or no erection was achieved and the patient discontinued attempts to achieve one. Patients filled out the remaining questions in their event logs, including whether the erection lasted long enough for successful intercourse, at a convenient time after sexual activity. Sexual activity was to be attempted a minimum of 2 times weekly. The International Index of Erectile Function was administered at baseline and end of double-blind treatment (4 weeks) or at the time of discontinuation.

**Statistical Analysis**

The time to the onset of erection that resulted in successful intercourse was analyzed at the end of the double-blind treatment phase. The analysis was based on the time recorded by patients in the event log for those patients experiencing at least one erection considered hard enough for intercourse and that lasted long enough for successful intercourse. The Wei, Lin, Weissfeld marginal model was applied to assess the treatment effect on the distribution of the time to onset with covariates as appropriate. The treatment effect (beta), standard error, P value, risk ratio, and 95% confidence interval for the risk ratio were determined. The median time to onset for each treatment group was estimated using the Cox proportional hazards regression model incorporating the covariates of age, smoking status, ED etiology, and ED duration. The cumulative percentage of patients experiencing at least one erection resulting in sexual intercourse during double-blind treatment for the 2-minute intervals between 12 and 30 minutes were compared between treatment groups, and the corresponding P values from the Pearson chi-square test were determined.

The International Index of Erectile Function variables (15 questions and 5 domain scores) were analyzed using an analysis of covariance model, including the terms for the treatment group and five covariates, baseline value, age, smoking status, ED duration, and ED etiology. All statistical tests were two-sided and performed at the 5% significance level.

**RESULTS**

**Patients**

A total of 228 patients with ED were randomized and received double-blind treatment with 100-mg sildenafil (n = 115; mean ± SD age 61 ± 10 years) or matching placebo (n = 113; mean ± SD age 59 ± 11 years). In addition to age, the treatment groups were similar with regard to ED duration, etiology, and severity (Table I). More than 95% of patients (n = 111 for sildenafil and n = 108 for placebo) completed the double-blind study. The reasons for discontinuation included patient withdrawal (placebo, n = 1), non–treatment-related adverse events (sildenafil, n = 2), and other reasons (sildenafil, n = 2; placebo, n = 4).

**TABLE I. Erectile dysfunction characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 113)</th>
<th>Sildenafil (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ED duration (yr)</td>
<td>7.2 ± 5.4</td>
<td>6.8 ± 4.6</td>
</tr>
<tr>
<td>ED etiology (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Mixed</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>ED severity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (EF domain ≤10)</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Moderate (EF domain 11–16)</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Mild/moderate (EF domain 17–21)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Mild (EF domain 22–25)</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>No ED (EF domain 26–30)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*ns: ED = erectile dysfunction; EF = erectile function.

**FIGURE 1. Time to onset of erection resulting in successful intercourse: percentage of patients receiving 100-mg sildenafil (n = 115) or placebo (n = 113) by cumulative interval. *P = 0.0343; †P = 0.0011; ‡P = 0.0001.

**TIME TO ONSET OF ERECTION**

Compared with those receiving placebo, significantly more patients receiving sildenafil reported at least one erection that resulted in successful intercourse as early as 14 minutes after drug administration (Fig. 1). The median time to erection for all attempts that resulted in successful sexual intercourse was 36 minutes with sildenafil and 141 minutes with placebo (Table II). Patients treated with sildenafil were more than three times as likely to obtain an erection that resulted in successful intercourse than patients receiving placebo.

**SEXUAL FUNCTION**

Compared with placebo, sildenafil treatment was associated with significantly greater scores for all domains of the International Index of Erectile Function (Fig. 2).

**SAFETY**

During the double-blind phase, 29 (25%) of 115 sildenafil-treated patients and 15 (13%) of 113 placebo-treated patients reported 41 and 18 adverse
TABLE II. Median time to onset of erections that resulted in successful sexual intercourse

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Occasions* (n)</th>
<th>Median (min)</th>
<th>Risk Ratio (95% CI)</th>
<th>Beta (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>1200</td>
<td>36.3</td>
<td>3.49 (2.43-5.01)</td>
<td>1.25 (P&lt;0.0001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1184</td>
<td>140.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: CI = confidence interval.  
* Occasion defined as when the patient took study drug and recorded information in the sexual activity event log.

FIGURE 2. International Index of Erectile Function scores as a percentage of maximal domain scores at baseline (white bars, n = 224–226) and after 4 weeks of double-blind treatment for patients receiving 100-mg sildenafil (black bars, n = 112–114) or placebo (gray bars, n = 111–112). P <0.0001 for sildenafil versus placebo for all domains.

COMMENT

The results of the present study confirmed earlier reports and anecdotal accounts demonstrating that the time to onset of erection that led to successful intercourse often occurred much earlier than 1 hour after taking sildenafil. In fact, the time to onset of erection with sildenafil was significantly superior to placebo as early as 14 minutes after dosing, and most of the men with ED who took sildenafil were able to achieve at least one erection that resulted in successful intercourse within 20 minutes (51%) or 30 minutes (68%). Overall, the median time to the onset of an erection that resulted in successful intercourse was 36 minutes after taking sildenafil.

The time to the onset of action for orally administered phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, and tadalafil is dependent on each drug's rate of absorption and distribution through the systemic circulation. The time to maximal plasma concentration for these phosphodiesterase-5 inhibitors ranges from 0.7 hours for vardenafil, 10.8 hours for sildenafil, and 2 hours for tadalafil. The time to the onset of the erection determined in RigiScan studies using visual sexual stimulation for these three PDE inhibitors followed an analogous pattern (26 minutes after a 20- or 40-mg dose of vardenafil, 27 minutes after 50-mg sildenafil, and 45 minutes after 10-mg tadalafil). Although the at-home data in this study closely match the laboratory RigiScan data for sildenafil, in a clinical trial with a design similar to the present study, a significant effect was noted within 16 minutes after dosing for patients receiving 20-mg tadalafil (32% versus 15% for placebo, P = 0.012), with 52% of the men receiving tadalafil (35% for placebo, P <0.05) able to achieve at least one erection that resulted in successful intercourse within 30 minutes. A significant effect was also noted within 16 minutes after dosing for patients receiving 20-mg vardenafil (34% versus 24% for placebo, P <0.05) in an at-home double-blind study. Of the men receiving vardenafil, 48% (30% for placebo, P <0.0001) were able to achieve at least one erection that lasted long enough for successful intercourse within 25 minutes.

The design of the current study allowed the determination of the minimal time to the onset of erection leading to successful intercourse after taking sildenafil in men with ED who had been previously successfully treated with sildenafil. Sildenafil was taken at least 2 hours after eating, and sexual stimulation was begun immediately. Although the use of the stopwatch may have been too intrusive for some patients, the conditions were otherwise favorable for a sildenafil response. The individual patient response times under less restrictive circumstances may differ to some extent, but the findings suggest that the time to action for sildenafil falls well within a time frame that most couples will find acceptable.
CONCLUSIONS

For slightly more than one half of this population of prior sildenafil responders, the time to onset of an erection that led to successful sexual intercourse was within 20 minutes of sildenafil administration, suggesting that the onset of action of sildenafil can be less than 30 minutes in men with ED.

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REFERENCES