Erection hardness and satisfaction with rapid sildenafil dose escalation from 50 to 100 mg in men with erectile dysfunction

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ABSTRACT

Objective: To evaluate tolerance to sildenafil and erection hardness and satisfaction with rapid dose escalation from 50 to 100 mg in men presenting with erectile dysfunction (ED).

Materials and methods: An open multicenter study was carried out over a period of 8 weeks. Initial monitoring and wash-out phase lasted for 2 weeks, followed by 2 weeks of introductory treatment with 50 mg of sildenafil, followed by a 4-week phase of 100 mg. All patients were over 18 years of age and had been diagnosed with ED (score ≤ 25 on the International Index of Erectile Function (IIEF)) and met with administration criteria for 50 and 100 mg of sildenafil.

Results: Of the 125 patients included in the study (mean age 53 years ± 11.0), 117 (94%) participated in the tolerance analysis and 114 (97%) in the efficacy analysis. A total of 110 patients completed the study. IIEF-EF scores improved from 14.5 to 21.7 (49%) (P<0.001) in patients who received initial 50 mg dose. When dose was increased to 100 mg, scores improved from 21.7 to 25.2 (P<0.001) and improvement was 75% at the end of the study. In the Quality

CONTENT

Conflict of Interest:
The present study was financed by Pfizer de México without any type of binding lega.
of Erection Questionnaire (QEQ), there was 91 and 128% improvement with 50 and 100 mg, respectively. In the Sexual Experience Questionnaire (Sex-Q) erection improved from 36 to 60%. There was a 38 to 64% increase in sexual intercourse and overall intercourse satisfaction increased from 50 to 79%.

In the Sexual Encounter Profile (SEP) with the Erection Hardness Grading Scale (EHGS), efficacy was 75% with 50 mg and 89% with 100 mg. All patients whose dose was increased to 100 mg had a better response than those with 50 mg. SEP and EHGS correlation was $r=0.97$. The most common adverse effects were headache (15%), red face (8%) and nasal congestion (3%) at the beginning of treatment, and they did not become more pronounced when dose was increased to 100 mg.

**Conclusions:** After initial treatment with 50 mg of sildenafil, patients whose dose was increased to 100 mg showed greater improvement in erection hardness and satisfaction with no increase in side effects or their severity. A positive correlation between successful sexual intercourse with dose escalation to 100 mg and Grade 4 erection hardness was demonstrated.

**Key words:** Erectile dysfunction, sildenafil, optimization, escalation, erection, hardness, scale, Mexico.

**INTRODUCTION**

Sexual function is a complex process involving both biological and psychosocial factors. Erectile dysfunction (ED) is defined as the inability to achieve or maintain erection of sufficient quality to have satisfactory sexual intercourse. Worldwide, ED affects from 13-28% of men between the ages of 40 and 80 years, and its prevalence increases with age. Functional erection limitation in ED patients has an impact on their physical and emotional health and their social well-being. ED treatment is important in maintaining general health in men and erection hardness is a fundamental component of erectile function. In a study of more than 3500 men with ED in different countries, participants stated that the principle attribute desired in ED treatment is that which provides firm and rigid erections.

Sildenafil citrate is an enzymatic inhibitor that blocks 5-phosphodiesterase. When blocked, this enzyme impedes intracellular cyclic guanosine monophosphate (cGMP) degradation created by nitric oxide that allows relaxation of the corpora cavernosa smooth muscle, and so it promotes erection. Goldstein points out in his sildenafil study that men with ED are interested in improving their erectile function. ED treatment optimization promotes treatment adherence and facilitates optimum results for the patient. Optimization will depend on the quick adjustment to dose escalation and active participation of both the patient and the physician is required in order to select the most adequate dose for the degree of severity of dysfunction. It is clear that incorrect use of the medication and suboptimum dose are the main reasons for treatment discontinuation. Optimization of erectile response is
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The goal of ED treatment. Erection grade evaluation is based on the Erection Hardness Grading Score (EHGS) (Table 1). This scale is the easiest and most practical tool for clinical erection evaluation.9,10

The purpose of the present controlled clinical study was to compare sildenafil tolerance, efficacy and erection hardness satisfaction with rapid sildenafil dose escalation from 50 to 100 mg in ED treatment.

STUDY DESIGN

An open, multicentric study with rapid dose escalation from 50 to 100 mg of sildenafil was carried out on men with erectile dysfunction (ED). Study chronogram included a 2-week monitoring and wash-out period, 2 weeks initial treatment with 50 mg of sildenafil citrate, followed by 4 weeks of dose-escalated treatment of 100 mg. Total study duration was 8 weeks. Patients were asked to engage in sexual intercourse with sexual stimulation within the 2-week monitoring and wash-out period (visit 1/week 2) and baseline visit (visit 2/week 0).

Participating patients had to have engaged in at least 2 acts of sexual intercourse before initiating 50 mg sildenafil treatment. They were instructed to take the medication when they were going to have sexual activity with sexual stimulation and not to take more than 1 tablet per day. Upon medication tolerance evaluation on visit 3/week 2, dose escalation to 100 mg was indicated if there were no contraindications. Between visit 3/week 2 and visit 5/week 6 treatment was discontinued only if the patient did not tolerate the dose or presented with some adverse effect. In such a case the patient was removed from the study and not allowed to reduce the dose to 50 mg.

The study was carried out in accordance with established norms of Mexican health regulation and with local clinical research ethics committee guidelines.

PATIENT SELECTION

All patients were older than 18 years of age, involved in a stable heterosexual relationship, diagnosed with ED, met clinical criteria for being treated with 50 and 100 mg of sildenafil and were not taking any other 5-phosphodiesterase (PDE-5) inhibitor at the time of study commencement. Patients were excluded from the study if they were hypersensitive to the medication, if they had low blood pressure (<90/50 mmHg), high blood pressure (>170/110 mmHg), severe liver damage, history of retinitis pigmentosa, significant cardiovascular disease in the last 3 months including cardiac insufficiency, myocardi infarction, unstable angina, cerebral vascular accident, cardiac arrhythmias including auricular fibrillation, radical prostatectomy, brachytherapy, nitrate or nitric oxide donor use and history of optical neuropathy.

All patients signed letters of informed consent before carrying out any study procedure or sildenafil administration.

RESULT MEASUREMENT AND STATISTICAL METHOD

The primary objective was to evaluate the efficacy of quick adjustment of 50 mg dose to 100 mg based on the International Index of Erectile Function score in the area of erectile function (IIEF-EF).11,12 Secondary objectives included questionnaire application: IIEF, areas of orgasmic function (IIEF-OF); sexual desire (IIEF-SD); intercourse satisfaction (IS); and degree of overall satisfaction (IIEF-OS).

The Quality Erection Questionnaire (QEQ) evaluates erection hardness and erection quality in general.9 The Sexual Experience Questionnaire (SEX-Q) evaluates functional, emotional and social aspects related to erection, satisfaction and sexual relationship.13 The profile of sexual encounters is measured by means of the Sexual Encounter Profile (SEP) and grading scale by the Erection Hardness Grading Score (EHGS).11,12,14

All adverse events were registered. The two-tailed Student t test was used for efficacy criteria adjusting statistical significance to α P < 0.05. Secondary objectives were also analyzed with the two-tailed Student t test. Correlation coefficient was calculated between the variable of successful intercourse in the SEP questionnaire with the EHGS results. Safety analysis was calculated with descriptive statistics.

Table 1. Grading Scale for Erection Hardness Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Penis size does not increase</td>
</tr>
<tr>
<td>1</td>
<td>Penis size increases but is not firm</td>
</tr>
<tr>
<td>2</td>
<td>Penis is not sufficiently firm for penetration</td>
</tr>
<tr>
<td>3</td>
<td>Penis is sufficiently firm for penetration but not completely rigid</td>
</tr>
<tr>
<td>4</td>
<td>Penis is completely firm and rigid</td>
</tr>
</tbody>
</table>

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**RESULTS**

**PATIENT CHARACTERISTICS**

Patient characteristics are shown in Table 1. The study included 117 patients with ED who received 2 doses of sildenafil, 50 and 100 mg. A total of 110 patients (94%) finished the study. Seven were excluded because contact was lost with them during follow-up or because they did not wish to continue participating in the study. ED etiology was organic in 45% of patients, mixed in 27% and psychogenic in 28%. At the beginning of the study, 78 patients (71%) presented with some type of comorbidity. The most frequent types are shown in Table 2.

**ERECTILE FUNCTION IMPROVEMENT**

Mean IIEF-EF baseline was 14.5 (visit 1/week -2). When treatment was begun with 50 mg of sildenafil (visit 2/week 0) mean score improved to 21.7 (p < 0.001) representing a 49% increase. On visit 3/week 2 dose was increased to 100 mg and mean score improved from 21.7 to 25.2 (p < 0.001). This was a 73% improvement and was maintained throughout the study (Image 1). At the end of visit 5/week 6, mean score was 25.5 (75%).

IIEF-EF improvement was also accompanied by a significant improvement in the area of orgasmic function (IIEF-OF). On visit 3/week 2, mean score went from 5.7 to 7.6 (p < 0.001) with 50 mg, representing a 33% increase. With 100 mg, there was an increase from 7.6 to 8.2 (p<0.001) up to the end of visit 5/week 6, with an additional 45% improvement. In the area of sexual desire (IIEF-SD) mean score improved from 5.8 to 7.3 (p < 0.001), increasing 25%, and from 7.3 to 7.8 (p < 0.001) on visit 3/week 2. At the end of visit 5/week 6 mean score increased to 8.1, representing a 39% overall improvement (Image 2). Recuperation in the area of intercourse satisfaction (IIEF-IS) went from 6.6 to 9.8 (p < 0.001) and from 9.8 to 11 (p < 0.001) representing

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**Table 1.** Demographic Data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>53.3 (rango 25-75)</td>
</tr>
<tr>
<td>18-44</td>
<td>24 (20.5)</td>
</tr>
<tr>
<td>45-64</td>
<td>77 (65.8)</td>
</tr>
<tr>
<td>&gt;= 65</td>
<td>16 (13.7)</td>
</tr>
<tr>
<td>ED Etiology</td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>52 (45%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>32 (27%)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>33 (28%)</td>
</tr>
<tr>
<td>Comorbidity*</td>
<td></td>
</tr>
<tr>
<td>Hipertension</td>
<td>32</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29**</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9</td>
</tr>
<tr>
<td>BPH</td>
<td>8</td>
</tr>
</tbody>
</table>

*Comorbidity in > 5%  
**Includes type I and II Diabetes Mellitus
Satisfaction recuperation rate was 84\% (\textit{p}<0.001, \textit{n}=117) respectively. This represents a recuperation rate of 59 - 79\%. However, at the end of visit 5/week 6, total overall satisfaction recuperation rate was 84\% (Image 3).

In relation to erection quality (QEQ) there was a very important change in score. With 50 mg score went from 36 to 69 (\textit{p}<0.001) representing a 91\% improvement. With 100 mg score increased from 69 to 83 (\textit{p}<0.001) and there was 128\% rehabilitation in erection quality from visit 3/week 2. At the end of the study on visit 5/week 6, recuperation was 125\% (Image 4).

In regard to sexual experience (SEX-Q) in the areas of erection, satisfaction and intercourse the following results were obtained: in erection there was a response from 15 to 21 (\textit{p}<0.001) on visit 3/week 2 and from 21 to 25 (\textit{p}<0.001) at the end of visit 5/week 6; in relation to sexual intercourse there was a change from 7 to 10 (\textit{p}<0.001) at visit 3/week 2 and from 10 to 12 at the end of visit 5/week 6; in the area of personal satisfaction with intercourse there was a substantial increase from 13 to 20 (\textit{p}<0.001), and from 20 to 24 (\textit{p}<0.001) with a 50\% improvement at visit 3/week 2 and a 79\% improvement at the end of visit 5/week 6.

In the SEP evaluation of Question 3, Did your erection last long enough to have successful intercourse? 75\% of
patients showed improvement with 50 mg at visit 3/week 2 and 88% with 100 mg at visit 4/week 3.

Improvement was continuous (89%) up to visit 5/week 6 (Image 5). Correlating this question about sexual intercourse with erection hardness (EHGS) produced $r = 0.97$ (Image 6).

Adverse event (AE) related to medication presented in 36/117 (31%) of patients. The most frequent were headache in 18 patients (15%), red face in 10 (8.5%) and nasal congestion in 3 (2.6%). All AE were mild and moderate and did not increase with dose escalation from 50 to 100 mg. Details are shown in Table 3.

**DISCUSSION**

Sildenafil has been shown to be highly effective and well-tolerated in multiple randomized, double-blind, placebo controlled clinical trials for ED treatment. It has been pointed out in the literature that adherence to ED treatment with sildenafil promotes treatment optimization and therefore dose escalation is a very relevant aspect. It requires the collaboration of both the physician and patient to diagnose the degree of severity of ED and to determine firmness and rigidity levels of erection. By contrast of what happens during controlled clinical trials, in every day practice sildenafil is prescribed to patients without the proper information on how to use it and what kind of results to expect. Incorrect medication administration including suboptimum dose and absence of sexual stimulation have been the most common causes of poor response to sildenafil. Treatment optimization includes the correct indications in order to obtain the best results from the medication such as:

1. Emphasize that the medication only works under sexual stimulation.
2. It takes 30 to 60 minutes to begin to have effect.
3. For the majority of men, sildenafil begins to act from the first or second dose. Some men require more attempts in order to obtain the desired result.
4. If results are unsatisfactory after 6-8 attempts, the physician may indicate dose escalation to 100 mg.
5. Sildenafil is completely contraindicated in patients receiving nitrates.

Between 42% and 59% of patients that did not initially respond to sildenafil did have success after being re-educated on its correct usage and after dose escalation when necessary. It is recommended for the majority of patients to begin with 50 mg. Depending on tolerability, preexisting medical conditions or concomitant medication that can elevate plasmatic levels of sildenafil, initial dose can be 25 mg. In the present study the majority of patients benefited from dose escalation to 100 mg. The study population had a mean age of 53 years. ED etiology was organic in 72%, and the most common causes were high blood pressure and diabetes mellitus. These demographic data concur with reports in the literature, not only in Mexico but in other countries as well.

The questionnaires used in the present study - IIEF, QEQ, SEX-Q and EHGS - identified and included the many dimensions of sexual dysfunction and its treatment through the evaluation of the different erectile dysfunction perspectives. The high correlation level indicates that each of these instruments represents a significant contribution to the study of sexual medicine and its prudent application in every day practice will help provide optimum medical attention to the patient on the part of the physician. In 2004, a panel of experts defined ED treatment efficacy as “...the capacity of a pharmacological agent to achieve and maintain an adequate and firm erection” and they described an optimum response as “...complete and consistent erection maintenance...”

Clinical research on erection hardness (EHGS) has established a strong positive correlation between the different questionnaires such as the erection quality questionnaire (QEQ) and the IIEF in the areas of erectile function, orgasmic function, sexual desire and intercourse satisfaction.

Our results lend support to the correlation among these questionnaires. In the present study, a change in erection grade 2 or 3 at the beginning of treatment to grade 4 at the end of the study shows a statistically significant improvement in erectile function, intercourse

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**Table 3. Adverse Events (AE)**

<table>
<thead>
<tr>
<th>Adverse events (AE)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Red face</td>
<td>10 (8.5%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Overall redness</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Patients who did not continue due to AE</td>
<td>0</td>
</tr>
</tbody>
</table>

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[Image 5]

[Image 6]
satisfaction, emotional satisfaction and ED treatment satisfaction parameters. Grade 4 hardness is achieved with dose optimization depending on the severity of ED and treatment regularity.

Improvement at the beginning of treatment with 50 mg of sildenafil was documented through the IIEF in its different areas of IIEF-EF, IIEF-OF, IIEF-SD, IIEF-IS and IIEF-OS. Greater benefit was observed with dose escalation to 100 mg at visit 3/week2. There was a 79% improvement in the IIEF-EF suggesting a relation between better functional performance with sexual desire and overall satisfaction (84% at the end of visit 5/week 6). Buvat obtained similar results in a multicenter study carried out in France, Italy, Greece, Spain and England.20

The QEQ (quality of erection questionnaire) is a validated instrument made up of 6 questions for evaluating patient satisfaction with erection quality in relation to firmness and rigidity, initiation and duration. It evaluates the changes in erection quality in ED treatment.10 At visit 3/week 2 there was an increase in score from 36 to 69, at visit 4/week 4 and up to the end of visit 5/week 6 the response was 82. Expressed as percentage, improvement with 50 mg of sildenafil was 91% and with 100 mg was 128%, showing the benefits of this optimization regimen.

In the three areas of the SEX-Q questionnaire – erection, satisfaction and intercourse – improvement with 50 mg was observed and was greater when dose was increased to 100 mg. In particular the area of personal satisfaction with intercourse had a total recuperation of 79% at visit 5/week 6.

Correlation analysis between Question 3 of the SEP questionnaire, Did your erection last long enough for you to have successful intercourse? and EHGS produced a correlation of r = 0.97. This result scientifically shows a direct relation between erection firmness and rigidity with the possibility of having successful intercourse. This positive correlation is repeated between grade 4 erection (completely firm and rigid) and the evaluated results of intercourse satisfaction and general overall satisfaction (IIEF), making firmness and rigidity the principal objective in ED treatment.22,23

The study demonstrated the relation between grade 3 and 4 erection and sildenafil dose. Grade 3 erection was achieved with 50 mg (sufficiently firm for having intercourse but not completely rigid) in 755 of patients at visit 3/week 2. With 100 mg, 88% achieved grade 4 erection (completely firm and rigid) at visit 4/week 4. These results concur with those reported by Goldstein, Levinson and Kaminetzky.10,24,25

In conclusion, 75% of ED patients responded efficaciously to initial 50 mg of sildenafil. However, dose escalation to 100 mg was associated with a better response in grade 4 erection hardness and satisfaction in 88% of patients and there was no increase in adverse events or their severity. Therefore, ED treatment regularity and optimization with dose escalation to 100 mg should be considered for patients who have had suboptimum response to 50 mg of sildenafil in order to achieve grade 4 firmness and rigidity in erection which is the principal objective in ED treatment.

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