Brazilian Journal of Urology
Official Journal of the Brazilian Society of Urology
Vol. 27 (2): 148-154, March - April, 2001

EFFICACY AND SAFETY OF SILDENAFIL CITRATE FOR THE TREATMENT OF ERECTILE DYSFUNCTION IN LATIN AMERICA

S. GLINA, E. BERTERO, J. CLARO, R. DAMIÃO, G. FARIA, A. FREGONESI, J. JASPERSEN, A. MENDOZA, D. MATTOS JR., L.C. ROCHA, M. SOTOMAYOR, C. TELÕKEN, S. URETA, E. ZONANA, F. UGARTE

Albert Einstein Hospital; HSPE; EPM; São Paulo, Brazil; UERJ, Rio de Janeiro, Brazil; Clinica Rio Claro, SP, Brazil; Unicamp, Campinas, SP, Brazil; Hospital General de México, Hospital Médica Sur, México, HC, Curitiba, PR, Brazil, Instituto Nacional de Nutrición Salvador Zubirán, México, Santa Casa de Porto Alegre, Porto Alegre, RS, Brazil, Hospital Español de México, Hospital Central Militar, México, Hospital Angeles del Pedregal, México

ABSTRACT

In this 12-week, double blind, randomized, placebo-controlled, multicenter, parallel group, flexible-dose study of oral sildenafil, 245 patients were treated in 15 centers in Latin America (9 in Brazil and 6 in Mexico). Patients began treatment with a 50-mg dose of sildenafil or matching placebo that could be adjusted to 100 mg or 25 mg based on efficacy and tolerability.

One hundred twenty-four patients were randomized to receive sildenafil and 121 to receive placebo. The most common concomitant medical condition was unspecified essential hypertension in 24% and 29% of the patients in the placebo and sildenafil groups, respectively. Scores for the 2 primary efficacy variables, frequency of penetration and frequency of maintained erection (International Index of Erectile Function Question 3 and Question 4), were both significantly greater in the sildenafil group ($p < 0.001$) compared with the placebo group. The number of patients who felt the study drug had improved their erections (36% for placebo vs. 81% for sildenafil) and the mean proportion of successful attempts at sexual intercourse during the last 4 weeks (32% for placebo vs. 71% for sildenafil) was also significantly higher for patients receiving sildenafil ($p < 0.001$).

Sildenafil was well tolerated with only 1 discontinuation due to a treatment-related adverse event (headache). Mild headache and flushing were the most frequently reported adverse events. None of the 6 serious adverse events (5 in the placebo group vs. 1 in the sildenafil group) was considered to be related to treatment. In conclusion, sildenafil is a well tolerated and effective treatment for erectile dysfunction of psychogenic, organic, or mixed etiology in Latin American men.

Key words: erectile dysfunction; penile erection; impotence; treatment
Braz J Urol, 27: 148-154, 2001

INTRODUCTION

Viagra® (sildenafil citrate) was the first oral drug approved for the treatment of erectile dysfunction (ED) (1). It was approved in Brazil and Mexico on February 5, 1998, and April 29, 1998, respectively. At the present time, it is approved in more than 100 countries worldwide and available in more than 80 countries.

The safety and efficacy of sildenafil has been shown in clinical trials that were conducted primarily in the United States and Europe (1,2). Since the initial clinical trials, additional studies have been conducted in different countries ranging from Africa to Asia, but final results have not yet been published.

The prevalence of ED in South America is expected to increase 150% from the year 1995 to 2025 (3). This will result in a projected increase in the num-

ber of men with ED from 10.5 million to 26.1 million. Thus, a need exists for an effective and acceptable treatment for ED in Latin America. The objective of the present clinical trial was to evaluate the safety and efficacy of oral sildenafil administered over a 12-week period to Latin American men with ED of organic, mixed, and psychogenic etiology.

METHODS

Study Design

This was a double-blind, randomized, placebo-controlled, multicenter, parallel-group, flexible-dose study of oral sildenafil taken approximately 1 hour before sexual intercourse. The study was conducted at 15 clinics (6 in Mexico and 9 in Brazil). The total duration of the study was 16 weeks, with a 4-week run-in period and 12 weeks of drug treatment. Patients visited the clinic at screening (week - 4), at the start of the study (week 0), and at weeks 2, 4, 8, and 12. All patients began treatment with sildenafil 50 mg, which could be increased to 100 mg for lack of efficacy or decreased to 25 mg if adverse events occurred.

Patients

Approximately 250 patients were enrolled who met the following requirements: 1)- aged 18 years or more, 2)- documented clinical diagnosis of ED of more than 6 months' duration, 3)- in a stable relationship with a female partner for at least 6 months, and 4)- gave written informed consent. Patients were excluded if they had 1)- genital anatomic deformities; 2)- hormonal abnormalities (high prolactin or low testosterone levels); 3)- a major psychiatric disorder that was not well controlled by treatment; 4)- known history of alcoholism or substance abuse; 5)- history of major hematologic, renal, or hepatic abnormalities; 6)- ED following a spinal cord injury; 7)- diabetes with either poor glycemic control or untreated proliferative diabetic retinopathy; 8)- history of stroke, myocardial infarction, or significant cardiovascular disease within the previous 6 months; 9)- hypotension (blood pressure < 90/50 mm Hg) or hypertension (blood pressure > 170/100 mm Hg); 10)- concurrent use of nitrates or nitric oxide donors; and 11)- known history of retinitis pigmentosa.

The intent-to-treat population consisted of all the patients who were randomized, took at least 1 dose of study medication, and had at least 1 post randomization evaluation of the efficacy variable in question. The efficacy evaluated population consisted of all the patients who were randomized, completed the study, and answered the primary efficacy questions.

Efficacy Assessments

The efficacy of treatment was assessed using questions 3 and 4 from the International Index of Erectile Function (IIEF) (4,5) at baseline (week 0) and at the end of 12 weeks of treatment. These 2 questions from the IIEF most closely address the definition of ED by asking about the ability to achieve (Q3) and maintain (Q4) an erection. Q3 and Q4 were scored on a scale from 1 ("almost never/never") to 5 ("almost always/always") with 0 indicating "no attempt at intercourse." Efficacy was also assessed at 12 weeks using a global efficacy question (GEQ) asking if treatment improved their erections.

Patients maintained an event log about sexual stimulation and intercourse every time they took a dose of study drug and/or engaged in sexual activity. The event log included the date of medication/activity, whether study medication was taken, whether the subject had sexual stimulation ("yes" or "no"), and whether the subject had a successful sexual intercourse (responses: "yes", "no - erection did not last long enough," "no - other reason"). Their responses to these questions, including the proportion of successful attempts at intercourse, were also used to assess efficacy.

Safety Assessments

All observed or volunteered adverse events that occurred during treatment or within 7 days of the end of treatment were recorded. The investigator determined the severity of the adverse event and whether it was related to drug treatment. Serious adverse events were those that 1)- resulted in death, 2)- were life-threatening, 3)- resulted in hospitalization or prolongation of existing hospitalization, 4)- resulted

in a persistent or significant disability or incapacity, or 5)- resulted in a congenital anomaly or birth defect. The safety analyses included all patients who were randomized and took at least 1 dose of study medication.

Data Analysis

Adverse events were tabulated by body system and by severity (mild, moderate, or severe). Safety and efficacy data were summarized using appropriate descriptive statistics. Descriptive statistics were used to compare the 2 treatment groups for similarity with respect to demographic and event log variables. The questions from the IIEF were analyzed using univariate analysis of covariance methods. The GEQ was analyzed using logistic regression. The data collected in the event logs were analyzed in terms of the proportion of successful attempts at sexual intercourse, which was estimated using an analysis of covariance model. All tests of hypotheses were performed at the 5% significance level (2-sided).

RESULTS

Patient Demography

In 15 centers in Latin America (9 in Brazil and 6 in Mexico), 263 patients were screened and 245 patients were randomized to treatment (124 patients from Mexico and 121 patients from Brazil). One hundred twenty-four patients were randomized to sildenafil and 121 to placebo. The 2 groups had similar demographics with mean ages of 55 and 58 years for the placebo and sildenafil treatment groups, respectively (Table-1). Of the 245 patients who were randomized, 133 presented with at least one concomitant or concurrent disease or syndrome (65 in the placebo group and 68 in the sildenafil group). The most common concomitant medical conditions were unspecified essential hypertension, diabetes mellitus, and hyperplasia of the prostate (24%, 18%, and 7% vs. 29%, 24%, and 5% for the placebo and sildenafil groups, respectively) (Table-1). The most common concomitant medications were antihypertensives, insulin, and antidiabetic drugs (Table-1).

Table 1 *- Demographics of patient population.*

Characteristic	Patients Treated with Placebo (n = 121)	Patients Treated with Sildenafil (n = 124)
Mean age, y (range)	55 (27-84)	58 (28-85)
Time since diagnosis, y	3.7	3.4
Etiology of ED, n (% of patients)		
Organic	50 (41.3)	51 (41.2)
Psychogenic	18 (14.9)	25 (20.2)
Mixed	53 (43.8)	48 (38.7)
Common diseases/syndromes, n (% of patients)		
Hypertension, unspecified essential	29 (24)	36 (29)
Diabetes mellitus	22 (18)	30 (24)
Hyperplasia of prostate	8 (7)	6 (5)
Concomitant medications, n (% of patients)		
Antihypertensives	30 (24.8)	29 (23.4)
Insulin and antidiabetics	27 (22.3)	27 (21.8)
Beta-adrenoreceptor blockers	9 (7.4)	11 (8.9)
Hypnotics, sedatives, and anxiolytics	4 (3.3)	7 (5.6)
Anti-inflammatory analgesics	13 (10.7)	6 (4.8)
Diuretics	6 (5)	6 (4.8)
Drugs for hyperlipidemia	4 (3.3)	6 (4.8)

The highest dose of sildenafil and placebo was preferred by most of the patients. Of the 124 patients who started treatment with sildenafil 50 mg, 4 (3%) were taking 25 mg, 48 (39%) were taking 50 mg, and 71 (57%) were taking 100 mg at the end point of the study (last dose dispensed).

Efficacy

The 2 primary efficacy variables, ability to achieve an erection and ability to maintain an erection (IIEF Q3 and Q4), were both significantly greater in the sildenafil group ($P < 0.001$) compared with the placebo group (Figure-1). The secondary efficacy variables derived from the patient event logs and the GEQ supported the results of the primary analysis. The number of patients who felt the study drug had improved their erections (Figure-2A) and the mean proportion of successful attempts at sexual intercourse during the last 4 weeks (Figure-2B) was also significantly higher for patients receiving sildenafil ($P < 0.001$).

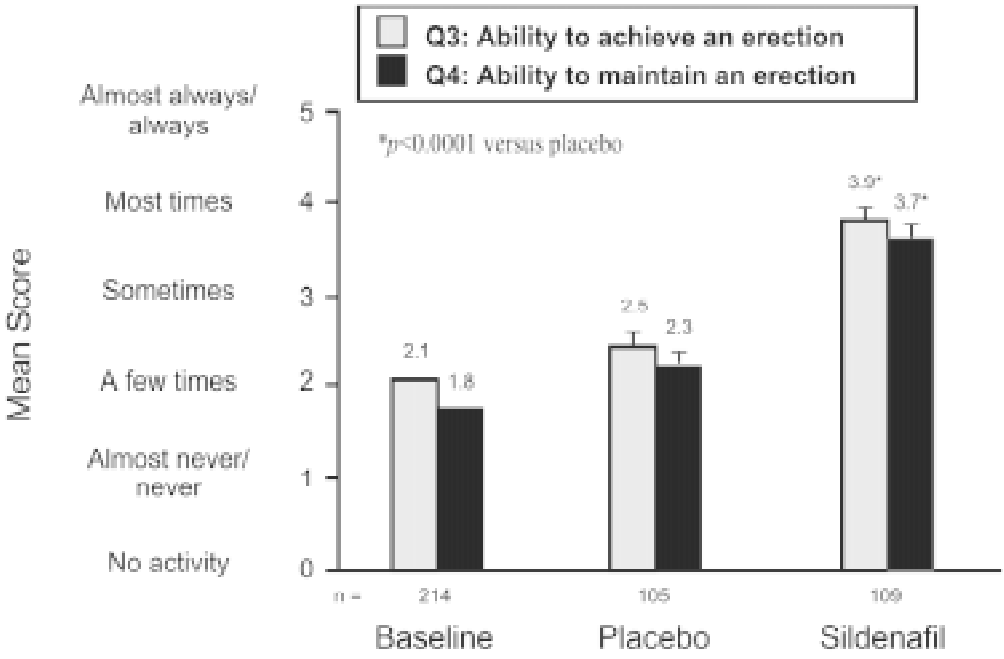

Figure 1 *- Mean scores for ability to achieve an erection (IIEF Q3) and ability to maintain an erection (IIEF Q4) for the intent-to-treat populations.*

Table 2 *- Reasons for discontinuation.*

	Patients Treated with Placebo n = 121 (%)	**Patients Treated with Sildenafil n = 124 (%)**
All causes	16 (13.2)	15 (12.1)
Related to study drug	3 (2.5)	4 (3.2)
Lack of efficacy	3 (2.5)	3 (2.4)
Adverse event	0	1 (0.8)
Not related to study drug	13 (10.7)	11 (8.9)
Adverse event	4 (3.3)	1 (0.8)
Other	9 (7.4)	10 (8.1)

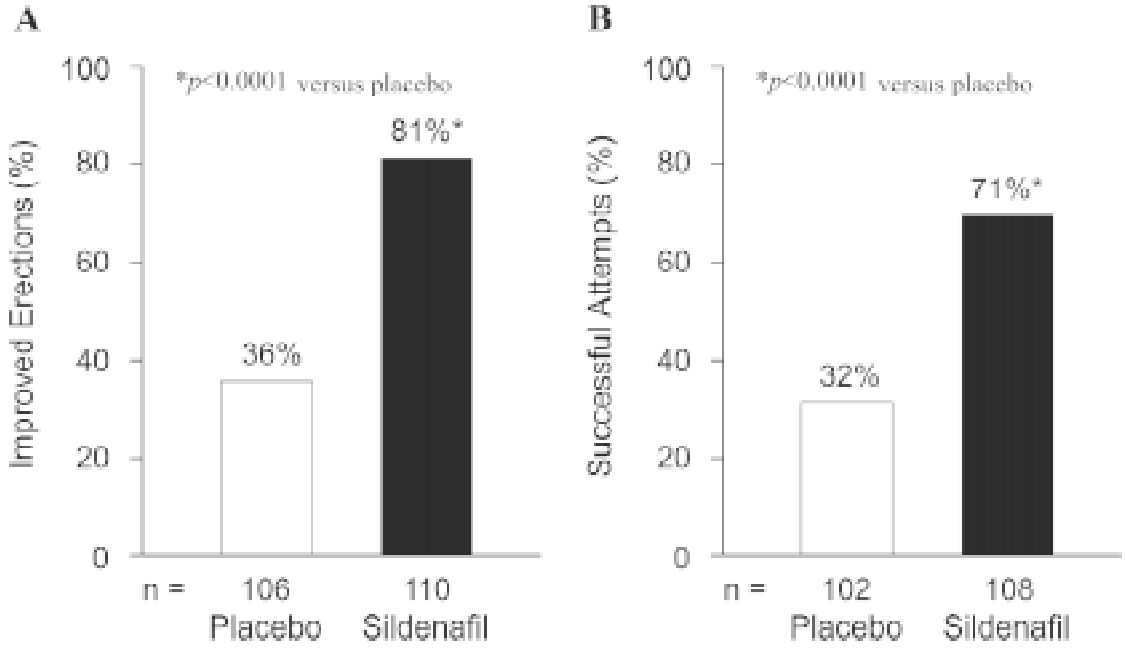

Figure 2 *- Patient-reported improvements with treatment for intent-to-treat populations. A)- Percentage of patients with ED reporting improved erections after treatment with placebo or sildenafil. The GEQ asked "Has the treatment you received improved your erections?" B)- Percentage of successful attempts at sexual intercourse reported in patient event logs during the last 4 weeks of the study.*

Safety

Fifteen (12%) of the patients receiving sildenafil discontinued the study compared with 16 (13%) of the patients receiving placebo (Table-2). Most of the discontinuations were not related to the study drug. Of those related to the study drug, 3 patients in both groups discontinued due to insufficient clinical response and 1 patient receiving sildenafil discontinued due to an adverse event (severe transient headache).

Forty-three (35%) of the patients receiving sildenafil had treatment-emergent adverse events of all causalities, with 36 (29%) considered treatment-related by the investigators (Table-3). This is con-

Table 3 *- Incidence of most common adverse events.*

	Patients Treated with Placebo n = 121 (%)		**Patients Treated with Sildenafil n = 124 (%)**	
	All Causality	**Treatment-Related**	**All Causality**	**Treatment-Related**
Flushing	0 (0)	0 (0)	11 (8.9)	11 (8.9)
Headache	6 (5.0)	4 (3.3)	15 (12.1)	11 (8.9)
Dyspepsia	0 (0)	0 (0)	9 (7.3)	8 (6.5)
Rash	0 (0)	0 (0)	5 (4)	4 (3.2)
Dizziness	1 (0.8)	1 (0.8)	4 (3.2)	4 (3.2)
Abnormal vision	1 (0.8)	1 (0.8)	4 (3.2)	4 (3.2)
Rhinitis	1 (0.8)	0 (0)	3 (2.4)	2 (1.6)

trasted with 24 (20%) of the patients receiving placebo reporting treatment-emergent adverse events of all causalities, with 7 (6%) being treatment-related. The most common all-causality adverse events were flushing and headache, occurring in 0% and 5% for placebo versus 8.9% and 12.1% for sildenafil, respectively. Most of the adverse events were considered mild, with 5 in the sildenafil group and 4 in the placebo group considered severe.

Ten patients (4 in the placebo group and 6 in the sildenafil group) had reductions in dosage due to adverse events (Table-4). The most common adverse event leading to a reduction in dosage was headache, which occurred in 2 patients in the placebo group and 4 patients in the sildenafil group. Six subjects (1 patient receiving sildenafil and 5 patients receiving placebo) had serious adverse events, but these were not considered to be related to the study medication (Table-5).

Table 4 - *Adverse events leading to reductions in dosage.*

	Patients Treated with Placebo n = 121 (%)	**Patients Treated with Sildenafil n = 124 (%)**
All causes	4 (3.3)	6 (4.8)
Headache	2 (1.7)	4 (3.2)
Flushing	0 (0)	1 (0.8)
Rhinitis	0 (0)	1 (0.8)
Gastrointestinal bleeding	1 (0.8)	0 (0)
Conjunctival hemorrhage	1 (0.8)	0 (0)

DISCUSSION

This is the first study to systematically evaluate the effects of sildenafil in Latin American men. The efficacy assessments demonstrate that sildenafil was significantly more effective than placebo at improving the symptoms of ED. Although the incidence of treatment-related adverse events was higher for sildenafil than for placebo (29% versus 6%, respectively), most of these (93%) were mild to moderate and only resulted in 1 discontinuation due to a treatment-related adverse event in a sildenafil-treated patient. Mild headache and flushing were the most frequently reported adverse events. None of the 6 serious adverse events was considered to be related to treatment. Thus, this study in 15 clinics in Brazil and Mexico demonstrates the safety, tolerability, and effectiveness of sildenafil for the treatment of ED in Latin American men.

An epidemiological study has examined the prevalence and associated risk factors of ED in men in northeastern Brazil (6), ranging from minimal to complete, was found in approximately 40% of 602 men sampled. The prevalence of ED was significantly associated with age, increasing from 28.5% for men between the ages of 40 and 44 years to 55.4% for men between the ages of 65 and 70 years. Other variables that were significantly related to ED included self-reported diabetes, depression, benign prostatic hyperplasia, caffeine consumption, and

Table 5 - *Incidence of serious adverse events.*

Treatment	**Patient History**	**Serious Adverse Event**	**Result**	**Treatment-Related**
Sildenafil	Diabetes mellitus	Visual alterations	Permanent discontinuation	No
Placebo	Chronic obstructive pulmonary disease	Pulmonary granuloma	Permanent discontinuation	No
Placebo	Inguinal hernia	Exacerbation of hernia	Permanent discontinuation	No
Placebo	None	Myocardial infarct	Permanent discontinuation	No
Placebo	None	Acute cholecystitis	Permanent discontinuation	No
Placebo	None	Multiple gastric ulcers	Temporary discontinuation	No

alcohol use. The authors concluded that ED is a common health problem among Brazilian men aged 40 to 70 years.

A Latin American epidemiological study conducted in Colombia, Ecuador, and Venezuela surveyed 1946 men older than 40 years of age (7). The authors reported prevalence of 19.8% and 33% for moderate-to-complete and minimal ED, respectively. Health-related risk factors associated with ED were hypertension, prostatic hyperplasia, diabetes, and associated medication. Thus, both epidemiological surveys confirm the need for an effective and well-tolerated treatment for ED in Latin American men. These studies also confirm that this studied population was representative of the general population in terms of concomitant medical conditions (e.g., diabetes and hypertension).

The results of this study are in agreement with previous clinical trials of sildenafil. Similarly reported that the highest dose of both sildenafil and placebo was preferred by most of the patients (74% for sildenafil and 95% for placebo) (1). This agrees quite well with the result in this study of 57% for sildenafil and 89% for placebo. Similarly, in previous clinical trials, (1,2) the most common adverse events that were considered treatment-related were headache, flushing, and dyspepsia, which is in agreement with the results reported here. In conclusion, this flexible-dose study suggests that oral sildenafil has similar efficacy and safety in Latin American men as in North American and European populations.

The research was supported by Pfizer Inc.

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Received: August 7, 2000
Accepted after revision: March 21, 2001

Correspondence address:
Dr. Sidney Glina
Hospital Albert Einstein
Rua Almirante Pereira Guimarães, 360
São Paulo, SP, Brazil
Fax: + + (55) (11) 3871-2466
E-mail: glinas@originet.com.br