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EFFICACY OF TADALAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION AT 24 AND 36 HOURS AFTER DOSING: A RANDOMIZED CONTROLLED TRIAL

HARTMUT PORST, HARIN PADMA-NATHAN, FRANÇOIS GIULIANO, GREG ANGLIN, LUCIO VARANESE, AND RAYMOND ROSEN

ABSTRACT

Objectives. To examine the therapeutic effects of tadalafil on erectile dysfunction (ED) at 24 and 36 hours after dosing.

Methods. A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 348 men (mean age 57 years) with ED was conducted in Europe and the United States. Patients were stratified by baseline severity of ED using the Erectile Function domain score of the International Index of Erectile Function and then randomly allocated within the severity group to receive tadalafil 20 mg (n = 175) or placebo (n = 173). Subsequently, participants were randomly assigned to two 4-week treatment intervals, during which they were requested to attempt sexual intercourse approximately 24 or 36 hours after tadalafil or placebo dosing. The primary outcome measure was the proportion of successful sexual intercourse attempts (completed to ejaculation) according to patient self-report using the Sexual Encounter Profile diary.

Results. Of the 348 patients, 327 (94%) completed the trial (163 of 175 in the tadalafil group and 164 of 173 in the placebo group). Thirty-six hours after tadalafil dosing, 59.2% of intercourse attempts were successful versus 28.3% in the placebo group ($P < 0.001$). The proportion of successful intercourse attempts at approximately 24 hours after treatment was also significantly greater with tadalafil (52.9%) than with placebo (29.1%; $P < 0.001$). Tadalafil was well tolerated. The incidences of four treatment-emergent adverse events were significantly greater in the tadalafil group than in the placebo group (all $P < 0.05$): headache, flushing, dyspepsia, and myalgia.

Conclusions. Tadalafil 20 mg is an effective and well-tolerated treatment for ED that has a period of responsiveness of up to 36 hours. UROLOGY **62:** 121–126, 2003. © 2003 Elsevier Inc.

Erectile dysfunction (ED) affects more than 150 million men worldwide,[1] including approximately 20 million European men and 30 million Americans.[1–3] Yet, reviews of published studies[4] have estimated that 70% of ED goes undiagnosed.

For the minority of these men who do seek help, therapy with the oral, selective phosphodiesterase 5 (PDE5) inhibitor sildenafil largely resolves ED, conferring benefits to both patients and their partners.[5–12] The efficacy of PDE5 inhibitors is ascribed to their ability to amplify the activity of the nitric oxide-3′,5′-cyclic guanosine monophosphate signaling pathway and to potentiate the smooth muscle-relaxing effects of nitric oxide within the corpus cavernosum.[13] However, despite its high efficacy rates, many men stop using sildenafil. The reasons for this include cost, adverse events, and perceived lack of efficacy.[14] In addition, in a survey about the importance of different outcome variables when choosing among pharmacotherapies for ED, the investigators found that success, avoiding a negative outcome, and naturalness ranked

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From Private Urological Practice, Hamburg, Germany; University of Southern California Keck School of Medicine, Los Angeles, California; Department of Urology, CHU de Bicêtre, Le Kremlin-Bicêtre, France; Eli Lilly Canada, Toronto, Ontario, Canada; Eli Lilly, Erl Wood, United Kingdom; University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, New Jersey.

Reprint requests: Hartmut Porst, M.D., Urological Practice, Neuer Jungfernstieg 6a, Hamburg 20354, Germany

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highest.[15] It is therefore possible that some men may discontinue sildenafil use because it makes sexual encounters feel less natural.

On closer examination, the perceived lack of efficacy of sildenafil can usually be attributed to inadequate dosing and failure by the physician to give thorough instructions (or of the patient to follow them).[16] For instance, some patients who are regarded as sildenafil failures may not have received sufficient sexual stimulation before attempting intercourse, and others may have attempted intercourse too early after dosing or after a high-fat meal.[16]

Tadalafil (Cialis, Lilly ICOS LLC, Indianapolis, Ind and Bothell, Wash) is a potent, reversible, and selective PDE5 inhibitor for the treatment of ED.[17] Compared with sildenafil (Viagra, Pfizer, New York, NY), tadalafil has an extended terminal half-life, 17.5 hours[18] versus 3.7 hours,[19] suggesting a lengthened period of responsiveness compared with sildenafil.

On the basis of the pharmacokinetic data, as well as preliminary clinical evidence suggesting an extended duration of action, this study was designed to evaluate the efficacy of tadalafil at 24 and 36 hours after dosing in men with ED.

MATERIAL AND METHODS

Study Design and Patient Population

This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 36 centers in Europe and the United States from February through April 2001. Ethical review boards approved its protocol and informed consent documents, and all patients and partners provided written informed consent before enrollment. The study consisted of a 4-week treatment-free run-in period (during which patients qualified for randomization in part by attempting sexual intercourse at least four times), followed by randomization in a 1:1 ratio to tadalafil 20 mg or matching placebo for 8 weeks.

The treatment period was divided into two 4-week intervals, each of which began with the investigator dispensing two doses of treatment for at-home use. Each man was instructed to take one dose of treatment before sexual activity, with no restrictions on alcohol or food intake. During one 4-week phase, the patients were to attempt sexual intercourse twice in conjunction with medication use, each time at approximately 24 hours after dosing, with an 8 to 10-day washout period between attempts.

In the other 4-week interval, men were instructed to attempt intercourse at approximately 36 hours after dosing, and then repeat after another 8 to 10-day washout period. Patients were also randomized into two order groups, with intercourse requested either 36 hours after dosing for the first 4-week interval, and then 24 hours after dosing for the second, or vice versa.

Men aged 18 years or older with a minimum 3-month history of ED who were in a stable, monogamous relationship with a female partner were eligible for enrollment. ED was defined as a consistent change in the quality of erection that adversely affected the patient's satisfaction with sexual intercourse. Patient exclusion criteria included the presence of penile implants or clinically significant penile deformities, failure to achieve erection after radical prostatectomy or pelvic surgery, a history of stroke or spinal cord trauma in the previous 6 months, unstable cardiac disease, clinically significant renal insufficiency or hepatobiliary disease, and concomitant antiandrogen use or chemotherapy.

To ensure balanced allocation, patients were stratified by baseline ED severity according to their scores on the Erectile Function domain of the International Index of Erectile Function (IIEF),[20] with mild ED characterized by a score of 17 to 25, moderate ED by a score of 11 to 16, and severe ED by a score of 1 to 10. Although scores of 26 to 30 are indicative of no ED,[21] those entering the study with scores of 26 or greater were added to the mild group for classification purposes. Patients were randomized to tadalafil or placebo according to a computer-generated randomization table. At the screening visit (4 weeks before randomization), patients underwent a physical examination, 12-lead electrocardiogram, and laboratory tests. Vital signs (blood pressure and heart rate) were measured at each visit, and the physical examination was repeated at week 8 or at premature discontinuation, if necessary, at each investigator's discretion.

Outcome Measures

The proportion of "yes" responses to Sexual Encounter Profile (SEP) question 3 (SEP-Q3), "Did your erection last long enough for you to have successful intercourse? [yes/no]," represented the primary efficacy variable.

Adverse events reported by patients were recorded at each 4-week visit, classified by severity, and coded using the COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) dictionary. Investigators also assessed the relationship of each event to the study drug. The safety outcome measure was the incidence of treatment-emergent adverse events in the placebo or tadalafil group. Treatment-emergent adverse events were defined as events that first occurred or worsened after the baseline assessment.

Statistical Analysis

Each randomized patient was eligible for the efficacy analysis. The analysis of safety included all randomized patients. All analyses were performed with the patients included in the group to which they were assigned by random allocation. Patient baseline characteristics were summarized for each treatment group.

For continuous patient characteristics at baseline, the mean values by therapy group were compared using analysis of variance. The incidence of the categorical variables at baseline was compared using the Pearson chi-square test.

It was specified a priori that a sexual encounter that was recorded $\geq$20 hours or $\leq$30 hours after dosing was considered an eligible 24-hour encounter if it was the first encounter after dosing. Similarly, an encounter that was recorded $\geq$30 hours and $\leq$48 hours after dosing was considered an eligible 36-hour encounter if it was the first encounter after dosing. However, the data presented herein are for encounters made $\geq$22 hours or $\leq$26 hours after dosing for the 24-hour time point and for encounters made $\geq$34 hours or $\leq$38 hours after dosing for the 36-hour time point.

Two null hypotheses were tested in a sequential fashion. The first was that there was no difference between tadalafil 20 mg and placebo in terms of the proportion of successful intercourse attempts at 24 hours after dosing, as measured by SEP-Q3. To reject this null hypothesis, significance at the 0.05 level was required. A second null hypothesis was tested only because the first null hypothesis was rejected with $P < 0.05$: that there was no difference between tadalafil 20 mg and placebo in terms of the proportion of successful intercourse attempts at 36 hours after dosing, as measured by SEP-Q3. To reject this

TABLE I. *Baseline demographic characteristics*

Characteristic	Placebo (n = 173)	Tadalafil (n = 175)
Age (yr)		
Mean	57	57
Range	28–87	22–80
Race (n)		
White	164 (95)	162 (93)
African	2 (1)	8 (5)
Hispanic	7 (4)	4 (2)
Other	0	1 (0.6)
Severity of ED* (n)		
Mild	69 (40)	70 (40)
Moderate	43 (25)	45 (26)
Severe	61 (35)	60 (34)
ED etiology (n)		
Organic	92 (53)	78 (45)
Psychogenic	18 (10)	23 (13)
Mixed	63 (36)	74 (42)
Current smoker (n)	40 (23)	43 (25)
Current alcohol use (n)	106 (61)	100 (57)

KEY: ED = erectile dysfunction.
Numbers in parentheses are percentages.
**Based on Erectile Function domain scores on the International Index of Erectile Function (mild, 17–30 [includes men with no ED, scores of 26–30]; moderate, 11–16; severe, 1–10).*

null hypothesis, significance at the 0.05 level was required. Each test was two-tailed.

For primary efficacy analyses of SEP-Q3, the "yes"/"no" responses were considered in a categorical repeated-measures model. The model included terms for treatment group, investigative site, patient's baseline percentage "yes" responses to SEP-Q3, and the baseline value of the Erectile Function domain of the International Index of Erectile Function. One model was fitted for the responses for the 24-hour time point, and a separate model was fitted for the responses for the 36-hour time point.

Safety was assessed by evaluating all reported adverse events, vital signs, and physical examination results. Treatment-emergent adverse events were summarized by the COSTART preferred term for severity and relationship to study drug. The analysis comparing the incidence of treatment-emergent adverse events among treatment groups was performed using Fisher's exact test.

RESULTS

Of 348 men enrolled, 327 (94%) completed treatment. The baseline characteristics were well balanced in the two treatment groups (Table I). The mean age in each group was 57 years, and most patients had ED for more than 1 year. On the basis of previously established Erectile Function domain categories of the International Index of Erectile Function, about 40% of men had mild ED, 35% had severe ED, and 25% had moderate ED.

Tadalafil was effective for 36 hours, with 132 (59%) of 223 intercourse attempts successfully completed in patients randomized to the 20-mg dose compared with 60 (28%) of 212 in those assigned to placebo ($P < 0.001$; Table II). On the basis of positive responses to SEP-Q3, 120 (53%) of 227 intercourse attempts at 24 hours were successfully completed in the tadalafil group compared with 72 (29%) of 247 in the placebo control group ($P < 0.001$). Of the patients randomized to placebo (n = 173), 144 had a sexual attempt at 24 hours and 128 at 36 hours. Approximately 37% and 35% of these patients had a successful attempt at 24 and 36 hours after dosing, respectively. Among those randomized to tadalafil (n = 175), 138 and 131 patients had eligible encounters at 24 and 36 hours after dosing, respectively. Of those, 61% had a successful intercourse attempt at 24 hours and 64% had a successful intercourse attempt at 36 hours ($P < 0.001$).

ADVERSE EFFECTS

Treatment with tadalafil was well tolerated. The incidences of treatment-emergent headache, flushing, dyspepsia, and myalgia were significantly greater in the active-treatment arm compared with the placebo group (Table III). Notably, there were no visual-perceptual changes, cardiovascular events, or any clinically significant effects of tadalafil on electrocardiographic findings, heart rate, or blood pressure.

The majority of adverse events were mild or moderate in severity. A total of 4 patients discontinued the study prematurely because of adverse events: 3 (2%) in the tadalafil group and 1 (0.5%) in the placebo group. Of the 3 patients taking tadalafil who withdrew, 1 each experienced myalgia (with lethargy) after two doses; dyspepsia after one dose; or abdominal pain (with nausea) after one dose. One placebo recipient experienced dizziness and headache.

COMMENT

Because of their relatively short half-lives, pharmacologic agents for ED have historically been used just before a couple engages in sexual activity, inextricably linking the medication with a man's sexual performance. For example, with alprostadil injection (Caverject, Pharmacia & Upjohn, Peapack, NJ), erection is expected to occur within 5 to 20 minutes after dosing and to last up to 1 hour, regardless of sexual stimulation.[22] With the alprostadil urethral suppository (MUSE, Vivus, Mountain View, Calif), erection is expected to occur within 10 minutes of administration and to last for 30 to 60 minutes, with or without sexual stimulation.[23] With sildenafil (Viagra, Pfizer, New York, NY), men may experience erection between 30 minutes and 4 hours after ingestion, and sexual stimulation is required.[24] For apomorphine (Ixense, Takeda Europe Research & Development

TABLE II. *Effects of tadalafil on successful intercourse completion over time**

	Placebo (n = 173)			Tadalafil (n = 175)		
Time Point	Intercourse Attempts (n)	Successful Intercourse Attempts (n)	Patients Reporting Successful Intercourse (%)	Intercourse Attempts (n)	Successful Intercourse Attempts (n)	Patients Reporting Successful Intercourse (%)
24-hr	247	72† (29.1)	36.8†	227	120† (52.9)	60.9†
36-hr	212	60† (28.3)	35.2†	223	132† (59.2)	64.1†

Numbers in parentheses are percentages.
**Proportion of successful intercourse attempts according to Sexual Encounter Profile Question 3 (SEP-Q3). For the requested 24-hr time point, first attempts made ≥22 hr and ≤26 hr after dosing were included; for the requested 36-hr time point, first attempts made ≥34 hr and ≤38 hr after dosing were included.*
†*P <0.001 for comparison (tadalafil vs. placebo) from a repeated-measures logistic regression model of yes/no responses to SEP-Q3 for requested encounter.*

TABLE III. *Incidence of adverse events**

Event	Placebo (n = 173)	Tadalafil (n = 175)	*P* Value
Headache	2 (1.2)	14 (8.0)	0.003
Flushing	0	10 (5.7)	0.002
Dyspepsia	0	9 (5.1)	0.004
Myalgia	0	6 (3.4)	0.030

Data presented as number of patients, with the percentage in parentheses.
**Treatment-emergent adverse events of all causes either occurring in at least 3% of each treatment group or exhibiting a significant difference across treatment arms.*

Centre, London, United Kingdom), men may experience erection 20 minutes after sublingual administration, provided they have adequate sexual stimulation, and can take a subsequent dose 8 hours later.[25]

In this trial, the ability of tadalafil to significantly increase the percentage of successful intercourse attempts was still evident 36 hours after dosing, with approximately 60% of intercourse attempts successfully completed at this time point versus 28% with placebo ($P < 0.001$). Tadalafil was well tolerated and exhibited a tolerability profile consistent with previously published data.[17]

This was not a study of efficacy per se or the time of maximum efficacy; rather, it was designed to determine whether tadalafil was associated with a treatment effect that could be discriminated from the effect of placebo for at least 24 and 36 hours. Standardized efficacy trials showed that approximately 75% of intercourse attempts were successful (as measured by SEP-Q3) among men treated with tadalafil 20 mg ($P < 0.001$ versus placebo), with 80% success for attempts undertaken up to 24 hours after dosing.[18] Differences among the rates of successful sexual intercourse with tadalafil in this study compared with standardized efficacy trials are likely related to the study's design. In the standardized efficacy trials, men were allowed to take tadalafil at any time of their choosing before engaging in sexual activity. In this trial, patients and their partners were required to wait a prespecified amount of time before engaging in sexual activity, causing them to plan their sexual encounters rather than allowing them to occur spontaneously.

Prior studies[18] using successful intercourse completion (SEP-Q3) as the primary outcome measure demonstrated that the earliest time to the onset of significant effects for tadalafil 20 mg was 16 minutes after dosing (32% success rate versus 15% with placebo; $P < 0.05$). At 30 minutes after dosing, 52% of men were considered responders to treatment versus 35% in the placebo group ($P < 0.05$).

The extended period of responsiveness afforded by tadalafil, which has a terminal half-life of 17.5 hours, may begin to change the treatment paradigm for men with ED. Unlike currently available treatments, tadalafil may, for example, enable a patient to take a pill on a Friday evening and have intercourse with his partner on Saturday night or Sunday morning. The broad therapeutic coverage conferred by tadalafil, which can be taken without restrictions on alcohol or food intake, might translate to enhanced convenience and simplicity of administration, traits that are valued by men with ED.[15]

CONCLUSIONS

The advent of a pharmacologic agent such as tadalafil, with a period of responsiveness that begins soon after dosing and lasts up to 36 hours, may allow men and their partners more freedom in the timing of their sexual activity.

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EDITORIAL COMMENT 1

The world of ED changed forever at the 1983 American Urological Association meeting in Las Vegas, when a British physiologist named Giles Brindley stepped from behind the podium and lowered his pants, revealing to colleagues his phentolamine-induced erection. Said one pundit of this watershed event, "Farther down the Strip, Siegfried and Roy were making a white Bengal tiger disappear, and two circus aerialists—one sitting on the other's shoulders—were traversing a tightrope without a net. But even in Vegas they'd never seen a show like *this*." Thus was crystallized the enduring principle that penile erection is caused by smooth muscle relaxation in the corpora cavernosa. Few breakthroughs in medical history have been heralded with the dramatic impact of Brindley's moment in Nevada.

Tadalafil (Cialis, Lilly ICOS LLC), along with sildenafil (Viagra, Pfizer) and vardenafil (Levitra, Bayer), belong to an orally effective class of smooth muscle relaxants called phosphodiesterase (PDE) inhibitors. Unlike Brindley's direct-acting phentolamine, PDE5 (penile) inhibitors produce erections indirectly, by inhibiting breakdown of cyclic guanosine monophosphate, the neurotransmitter for corporal smooth muscle relaxation. Thus, with PDE5 inhibitors, erection develops in a physiologic manner by amplification of the nitric oxide pathway and only with sexual stimulation. Sildenafil, the sole PDE5 inhibitor currently approved in the United States, has enjoyed enormous success because of its specificity, effectiveness, convenience, and safety; according to Pfizer, more than 20 million men in 110 countries have used the drug.

In the present report of Phase III tadalafil data, 348 men with organic and/or psychogenic ED were given the drug (20 mg) or placebo in an 8-week randomized, multicenter trial. The trial was designed specifically to test the duration of action of the drug. Thirty-six hours after dosing, approximately two thirds of tadalafil patients, but only one third of placebo patients, were able to have successful intercourse ($P < 0.001$). Side effects were uncommon and not severe, including mostly the now-familiar headache, flushing, and dyspepsia. A few patients also reported myalgias, possibly because of skeletal muscle PDE inhibition. Only 3 of 175 tadalafil patients discontinued the trial prematurely because of adverse events. Thus, the data support the authors' statement that tadalafil is effective and well tolerated.

What distinguishes tadalafil pharmacologically is its long duration of action, relative selectivity for PDE5, and bioavailability independent of food intake. The drug has a half-life of 17.5 hours compared with 4 hours for sildenafil, earning tadalafil the nickname "weekender." Clearly, tadalafil could be taken on Friday and continue to enhance erectile function for at least the next several days without redosing. This convenience must be weighed against the possibility of a lingering undesirable effect in some men. In Europe, where the drug was approved in November 2002, the package leaflet carries a stern warning ("Do not take Cialis") not only for men using organic nitrates and nitric oxide donors, but also men with serious heart disease, recent stroke or myocardial infarction, and uncontrolled blood pressure (high or low). The Viagra warning is similar.

Just how tadalafil will fit into our therapeutic armamentarium vis-à-vis other PDE5 inhibitors (and future remedies unknown) will not become clear until the widespread use expected after Food and Drug Administration approval. What is clear, however, is that the pre-Brindley world of ED—a world largely consisting of testosterone injections, psychotherapy,