Efficacy of Udenafil for the Treatment of Erectile Dysfunction up to 12 Hours after Dosing: A Randomized Placebo-Controlled Trial

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ABSTRACT

Introduction. Udenafil is a newly developed selective phosphodiesterase type 5 inhibitor for the treatment of men with erectile dysfunction (ED).

Aim. To evaluate the efficacy of udenafil in treating ED for up to 12 hours after dosing.

Methods. This was a randomized, double-blind, placebo-controlled, parallel-group, fixed dose design, multicenter study. Following a 4-week nondrug baseline period, 104 men with ED of broad etiology and severity were randomized to one of two treatment groups: udenafil 100 mg or placebo. Participants were requested to attempt sexual intercourse at 12 hours after udenafil or placebo dosing during a 4-week treatment period.

Main Outcome Measures. The primary efficacy variable was the response of patients to question 3 of the Sexual Encounter Profile (SEP Q3). The secondary efficacy measures were the response of patients to question 2 of the Sexual Encounter Profile (SEP Q2). Additional secondary efficacy measures included changes from baseline in the erectile function (EF) domain scores of the International Index of Erectile Function (IIEF) questionnaire.

Results. Of the 104 patients, 103 (50 in the udenafil group, 53 in the placebo group) completed the study. Udenafil significantly enhanced the rate of maintenance of erection (SEP Q3; placebo, 28.3% vs. udenafil, 54.7%; P < 0.0001). Significant change from baseline in the IIEF-EF domain was observed in the udenafil group (placebo, –0.58 ± 0.67; udenafil, 4.40 ± 0.84; P < 0.0001). For SEP Q2, there was no difference from baseline and no difference between the two groups. The overall adverse events rate was 11.3%. Most adverse events were mild or moderate in severity, and no serious adverse events were reported during the study and the follow-up period.

Conclusions. Udenafil at 100 mg was effective for relieving ED for up to 12 hours after dosing. This duration of effectiveness could allow for flexibility and spontaneity in the sexual lives of patients. Park HJ, Park JK, Park K, Min K, and Park NC. Efficacy of udenafil for the treatment of erectile dysfunction up to 12 hours after dosing: A randomized placebo-controlled trial. J Sex Med 2010;7:2209–2216.

Key Words. Erectile Dysfunction; PDE5; Long-Acting PDE5 Inhibitor; Udenafil; Clinical Trial

Introduction

Since the successful introduction of sildenafil (Viagra, Pfizer, New York, NY, USA), oral agents have been considered a standard modality for treating men with erectile dysfunction (ED). Following sildenafil, vardenafil (Levitra, Bayer HealthCare, Leverkusen, Germany), and tadalafil (Cialis, Lilly ICOS LLC, Indianapolis, IN, USA) have been introduced. These two phosphodiesterase type 5 (PDE5) inhibitors have shown good efficacy and safety, similar to that of sildenafil [1,2]. In addition to these three PDE5 inhibitors, udenafil (Zydena, Dong-A, Seoul, Korea) and mirodenafil (M-vix, SK Chemicals, Seoul, Korea) are also available in Korea as effective treatment options for ED [3,4]. Each PDE5 inhibitor shares a mechanism that inhibits PDE5, and thereby induces penile erection. However, there are variations in the onset of action and duration of action.
between the agents, which are selected according to their own medication features of each agent by physicians. From the patient’s perspective, specific agents tend to be favored according to their own sexual behavior. These factors affect the prescriptions made by physicians [5].

One recent change in the pattern of PDE5 inhibitor administration is that of low dose daily or regular dosing. Evidence from basic scientific investigations has indicated that daily doses PDE5 inhibitors might improve erectile function (EF) and show a number of beneficial effects on the penile corpus cavernosum [6]. Moreover, from the patient’s viewpoint, sexual intercourse can be performed without time concerns. This can provide confidence and satisfaction to patients who tend to compare treatment outcomes with their previous experience of spontaneous, unscheduled sexual intercourse attempts prior to developing ED [7]. Further study on the duration of action of PDE5 inhibitors is needed for low dose daily or regular dosing applications of PDE5 inhibitors. According to preclinical studies, the pharmacokinetic profiles of udenafil include a Tmax of 0.8–1.3 hours and a T1/2 of 7.3–12.1 [8–10]. However, the duration of action has not been thoroughly investigated through clinical study. Practical knowledge of the time window available for sexual intercourse would be valuable for couples planning sexual activity. Given this background, this study was conducted to evaluate the efficacy of udenafil on ED for up to 12 hours after dosing.

Methods

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study conducted at four different centers located in Korea in accordance with guidelines of the Good Clinical Practice and International Conference on Harmonization, and in conformity with the ethical principles of the Declaration of Helsinki. Patients included in the study were recruited prospectively and consecutively from four urology centers. Written informed consent was obtained from each patient prior to randomization. Prior use of other PDE5 inhibitors was allowed, but patients who had not responded to them were excluded from this study. Initially, eligible patients had a 4-week, treatment-free run-in period during which time they were required to have attempted intercourse on at least four separate days and must have been unsuccessful in at least half of these attempts. Subsequently, patients were assigned randomly to receive either placebo or udenafil at 100 mg. Based upon results of phase I and II trials on udenafil, patients were allowed to take investigational products ( udenafil or placebo) when necessary, with water 12 hours prior to sexual intercourse, but not to exceed one dose per day in this trial [9,10]. During the 4-week treatment period, each patient’s tolerance and response to the study drug were recorded in diaries. The quantity of drug taken, number of attempts to have sexual intercourse, and primary and secondary efficacy variables were recorded. The diaries were distributed on visits 1 and 2. On the first visit, the patients were instructed on how to write the diary. The diaries were completed during the trial, submitted at the next visit and reviewed on visits 2 and 3. A follow-up contact was also made 6 or 7 days after the 4-week treatment phase for assessment of any additional adverse events.

Subjects

Men aged 19–70 years old, with at least a 6-month history of ED of organic, psychogenic, or mixed etiology, and in a stable, monogamous relationship with a female sexual partner were recruited. Men with the following conditions were excluded from the study: penile anatomic defects; spinal cord injury; radical prostatectomy or radical pelvic surgery; a primary diagnosis of another sexual disorder; hyperprolactinemia; a low level of total testosterone; poorly controlled diabetes or proliferative diabetic retinopathy; a major uncontrolled psychiatric disorder; a history of active peptic ulcer disease within 1 year of screening; a history of major hematological, renal, or hepatic abnormalities; a recent (within the previous 6 months) history of cardiovascular disease, stroke or myocardial infarction; cardiac failure; unstable angina and life-threatening arrhythmia or a history of alcoholism or substance abuse. Patients were also ineligible if they were receiving regular treatment with nitrates, anticoagulants (except for low-dose aspirin), androgens, antiandrogens, or trazodone. Prior use of other PDE5 inhibitors was allowed, but patients who had not responded to them were excluded from this study. Concomitant use of other therapies for ED was prohibited. Taking erythromycin, cimetidine, ketoconazole, indinavir, or grapefruit juice were avoided during the study to minimize possible drug interactions.
Primary Efficacy Outcome Variable
The primary efficacy variable was the response of patients to question 3 of the Sexual Encounter Profile (SEP Q3: Did your erection last long enough for you to complete intercourse with ejaculation?), which was assessed after each attempt at intercourse following udenafil or placebo therapy.

Secondary Efficacy Outcome Variable
The Secondary efficacy measure was the response of patients to question 2 of the SEP (SEP Q2: Were you able to insert your penis into your partner’s vagina?), which was assessed after each attempt at intercourse with udenafil or placebo therapy. Additional secondary efficacy measures included any change from baseline in the EF domain scores of the International Index of Erectile Dysfunction (IIEF) questionnaire, calculated from comparison of total scores from questions 1–5 and 15 from the IIEF questionnaire assessed at baseline and after 4 weeks of udenafil or placebo treatment [11–13]. Comparative analyses were performed between the two groups regarding the efficacy variables.

Adverse Events and Safety
All adverse events were monitored and recorded during the study. For each adverse event, the investigator assessed seriousness, intensity (mild, moderate, or severe), and relationship to the study drug (definite, probable, possible, improbable, none, or impossible to evaluate). Vital signs (blood pressure and pulse in the sitting and standing positions) and clinical laboratory parameters (hematology, blood chemistry, and urinalysis) were evaluated at each visit. A 12-lead electrocardiogram was performed at screening (visit 1) and at week 0 (visit 2), and 4 (visit 3) of the treatment course.

Statistical Methods
All efficacy analyses were performed using data from the intention-to-treat population that included all randomized patients who had received at least one dose of the study drug and at least one valid postbaseline evaluation. The statistical analyses were performed using SPSS 12.0 software for Windows (Inc., Chicago, IL, USA). The proportion of “yes” responses to SEP Q2 and Q3 (i.e., the success rates) were analyzed using paired Student’s t-tests. Intergroup differences in the proportion of “yes” responses to SEP Q2 and Q3 were analyzed using the repeated measures analysis of covariance (RM ANCOVA) method with adjusted covariates or the contingency table method. Intergroup differences for the IIEF-EF domain were analyzed using the RM ANCOVA method with adjusted covariates. For safety analysis, 90% confidence intervals were used in listing the number of adverse events that occurred and the rate of patients experiencing adverse events. Intergroup comparisons were performed using Chi-square test or Fisher’s exact tests. Continuous laboratory data were analyzed using RM ANCOVA, and any changes of laboratory parameters from normal to abnormal were analyzed by group using McNemar’s test.

Results

Subjects
One hundred four patients were randomized initially and were eligible for the study population: 51 in the placebo group, and 53 in the udenafil group. Of these, one patient did not receive an efficacy evaluation after baseline because he withdrew consent, leaving 50 in the placebo group. At baseline, there were no statistically significant differences between the groups with respect to demographic or clinical characteristics (Table 1). Most patients in each treatment group had ED of organic or mixed etiology. Of all patients enrolled in this study, the IIEF-EF domain score at baseline was ≥11 in 94.1%, and 88.7% of patients in the placebo and udenafil groups, respectively. 58.8% of patients in the placebo group and 71.7% in the udenafil group had previous PDE5 inhibitor experience before entering this study. Hypertension was most common among the concomitant illnesses recorded.

Intercourse Attempts
One bottle of 20 tablets containing the study medications was provided to each patient ( udenafil 100 mg or placebo). The frequency of sexual intercourse attempts during the study period was 12.6 ± 5.3 and 14.1 ± 5.4 times in the placebo and udenafil groups, respectively. Two sexual intercourse episodes within 12 hours between dosing and intercourse attempts were reported in one patient (placebo group), and those episodes were excluded from analysis.

Primary Efficacy Outcome Variable
Patients treated with udenafil showed significantly greater improvement in mean per-patient propor-
tion of successful intercourse attempts (SEP Q3) than placebo-treated patients. The mean ability of each man to maintain an erection until completion of intercourse was 54.7% with udenafil compared with 28.3% for the placebo (Figure 1).

Secondary Efficacy Outcome Variable

SEP Q2

For SEP Q2, the mean per-patient proportions of successful penetration attempts were 73.2% for the placebo group and 82.3% for the udenafil group (Figure 2). Both patient groups showed improvements in mean per-patient rates of successful penetration. However, differences from baseline were not statistically significant in either group. There was also no difference between the two groups.

IIEF EF Domain

Analysis of differences in each group revealed that the udenafil group showed a statistically significant improvement in regard to change from baseline in the EF domain score of the IIEF (placebo, \(-0.58 \pm 0.67\) vs. udenafil, \(4.40 \pm 0.84\); \(P < 0.0001\)). When difference from baseline value was compared between visits, a statistically significant improvement was observed in the udenafil treatment group (\(P < 0.0001\) (Figure 3). However, no

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and baseline parameters for the ITT population</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo (N = 51)</td>
</tr>
<tr>
<td>Mean age: years*</td>
<td>52.24 ± 9.56</td>
</tr>
<tr>
<td>Height: cm*</td>
<td>168.8 ± 5.84</td>
</tr>
<tr>
<td>Weight: kg*</td>
<td>69.09 ± 9.37</td>
</tr>
<tr>
<td>History of ED: years*</td>
<td>3.4 ± 4.4</td>
</tr>
<tr>
<td>ED etiology: N (%)†</td>
<td></td>
</tr>
<tr>
<td>Organic</td>
<td>42 (82.35%)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>2 (3.92%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>7 (13.73%)</td>
</tr>
<tr>
<td>Severity of ED–EF domain score: N (%)‡</td>
<td></td>
</tr>
<tr>
<td>Severe (=11)</td>
<td>3 (5.88%)</td>
</tr>
<tr>
<td>Moderate (11–16)</td>
<td>21 (41.18%)</td>
</tr>
<tr>
<td>Mild-to-moderate (17–21)</td>
<td>26 (50.98%)</td>
</tr>
<tr>
<td>Mild (22–25)</td>
<td>1 (1.96%)</td>
</tr>
<tr>
<td>Prior other PDE5 inhibitors users: N (%)†</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (13.73%)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>7 (13.73%)</td>
</tr>
<tr>
<td>Central nervous system disorder</td>
<td>1 (1.96%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (15.69%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5 (9.80%)</td>
</tr>
<tr>
<td>Other endocrine and metabolic disorders</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Smoking history: N (%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (33.33%)</td>
</tr>
<tr>
<td>Non or ex-smoker</td>
<td>34 (66.67%)</td>
</tr>
</tbody>
</table>

*Values are expressed as the mean ± standard deviation. Evaluated by analysis of variance.
†Evaluated by Chi-squared test.
ITT = intention-to-treat; ED = erectile dysfunction; PDE5 = phosphodiesterase type 5.

Figure 1 Mean success rates per patient reporting the ability to maintain erections sufficiently to have successful intercourse at baseline and after 4 weeks. *\(P < 0.0001\) vs. placebo.

Figure 2 Mean success rates per patient reporting the ability to penetrate his partner at baseline and after 4 weeks.
significant improvement was observed in the placebo group. In addition, the percentage of patients who met the “return-to-normal” definition of the IIEF EF domain score was significantly higher ($P < 0.0001$) for the udenafil compared with the placebo group (6% for placebo and 24.5% for udenafil).

**Safety and Tolerability**

During the study, only one patient in the udenafil group discontinued treatment because of an adverse event (toothache). Most adverse events were mild or moderate in severity, and no serious adverse events were reported during the study or the follow-up period. Commonly reported treatment-related adverse events included stomach discomfort, flushing, headache, and nasal congestion (Table 2). No clinically significant changes in laboratory tests, electrocardiograms, or blood pressure were observed in either group.

**Discussion**

Udenafil has been developed in Korea as a selective PDE5 inhibitor, and its efficacy and safety have been well documented through several studies [3]. According to preclinical studies, udenafil has been reported to have a T1/2 of 7.3–12.1 hours [9,10]. However, this study is the first to perform a thorough evaluation of the duration of action of udenafil. The proportion of patients in the 100-mg udenafil group who responded “yes” to SEP Q3 (maintenance of erection), the primary efficacy variable, increased from 19.03% at baseline to 54.66% following a 4-week treatment period. There were significant improvements with udenafil treatment (35.63%) compared with placebo (10.23%). In particular, given a success rate of 70.08% for SEP Q3, which is known to occur in studies when udenafil at 100 mg is administered within 30 minutes to 8 hours prior to sexual intercourse [3], the success rate of udenafil administered 12 hours prior to sexual intercourse in this study, could be regarded as significant.

The secondary efficacy variable in this study, SEP Q2 (successful penetration) showed no significant difference following a 4-week treatment compared with baseline in both the study groups. This is not in agreement with studies conducted by Paick et al. [3], which showed that the success rate was significantly better than baseline following a 12-week administration of udenafil at 100 and 200 mg. The discrepancy between the responses to SEP Q2 and SEP Q3 is probably because of the relatively high success rates of baseline reported from the SEP Q2 (72.3% and 75%) compared with SEP Q3 (18.03% and 19.03%) in both groups. This means that the participants were most likely suffering from corporal veno-occlusive disease. The direct role of arterial disease as a cause of ED in this cohort might have been only secondary or largely limited. Another secondary efficacy variable, the EF domain scores of the IIEF, improved significantly by 28.6% following a 4-week treatment period compared with baseline in the udenafil group; however, this was not seen in the placebo group.

**Table 2**  Incidence of treatment-related adverse events (AEs)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Placebo (N = 50)</th>
<th>Udenafil 100 mg (N = 53)</th>
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<tbody>
<tr>
<td></td>
<td>Number of adverse events (number of patients)</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>2 (2)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

AEs = adverse events.
that the frequency of intercourse is closely correlated with sexual satisfaction [17]. Interestingly, one study showed that women’s preference were similar to those of men when using tadalafil or sildenafil, with some women preferring tadalafil because of relaxed, satisfying, and longer-lasting sexual experiences [18]. Although, the extent to which sexual behavior alters is not uniform across geographical regions [19], prior sildenafil citrate users modified their sexual intercourse and drug intake timing behavior when exposed to tadalafil with respective dosing instructions; the proportion of intercourse attempts per patient made >4 hours after dose was considerably higher during the tadalafil than the sildenafil treatment period [20]. These patients reported improvements in self-confidence, spontaneity and fewer time concerns. If patients could reduce their time concerns, the duration of action of PDE5 inhibitors would be an essential factor.

However, in contrast, it has been reported that despite their different pharmacokinetic profiles, the different uses of PDE5 inhibitors remain fairly similar [21].

There are not many specialized studies on the duration of action of PDE5 inhibitors. For sildenafil, the reported duration varies depending on the authors. It might be effective in a significant proportion of men with ED for up to at least 4 hours [22], 10 hours [23], or a maximum of 12 hours [24] after being taken. All of these data suggest that the duration of action of sildenafil substantially exceeds its terminal elimination half-life of approximately 4 hours [25]. Some molecular mechanisms have been proposed that could account for such prolonged action of PDE5 inhibitors. These include persistence of biochemical effects after the inhibitor is cleared from cells, and retention of the drug in penile vascular smooth muscle cells [26,27]. On the other hand, in the case of udenafil, its pharmacokinetic profiles include a Tmax of 0.8–1.3 hours and a T1/2 of 7.3–12.1 hours [9,10]. Therefore, it is possible that the effect would persist even longer than 12 hours, as shown in this study. Hence, further studies are warranted to examine the duration of action of udenafil, which is clearly longer than 12 hrs.

PDE5 inhibitors with a long duration of responsiveness provide patients with ED and their partners with a treatment option that can offer greater flexibility and potentially less anxiety surrounding the resumption of sexual activity. However, shorter-acting PDE5 inhibitors may be preferred by men or couples with concerns regarding the duration of side-effects. In our study, adverse events associated with udenafil were similar to those commonly observed in other studies on PDE5 inhibitors. These included stomach discomfort, flushing, headache, nasal congestion and toothache. Udenafil was not observed to induce myalgia or abnormalities in color vision, which is one of the profound side-effects of tadalafil and sildenafil [5]. This lack of adverse effects is associated with previously reported favorable pharmacokinetic profiles, including a greater selectivity of udenafil for PDE5 shown by in vitro studies [9,10].

Some limitations of the present study should be noted. First, we excluded patients who had not responded to prior oral PDE5 inhibitor treatment. The aim of this study was to evaluate whether the efficacy of usual dosage of udenafil (100 mg) would last up to 12 hours from administration. Therefore, hard-to-treat patients who need high doses of PDE5 inhibitors or self-injection therapy were not appropriate for the present study. Second, the short duration of study (4 weeks) is clearly a limitation, because this tends to either overestimate or underestimate drug efficacy rates. A final potential limitation of this study was that the causes of ED were not evaluated definitively in the subjects enrolled, resulting in the discrepancy between the responses to SEP Q2 and SEP Q3 in current study. This limitation also makes it unclear whether the results apply equally to patients with ED of different etiologies.

From the results evaluated thus far, the efficacy of udenafil treatment for ED at 12 hours after dosing is considerable. The fixed dose of 100 mg and treatment duration applied in our study may have limited the observed efficacy of udenafil. In addition, no significant differences in efficacy were observed in SEP Q2 in our study. Thus, larger clinical trials with longer treatment durations are warranted, applying a flexible dosing of udenafil in a more diverse group of patients.

Conclusions

Udenafil at a dose of 100 mg was effective and well tolerated in these patients with ED, with no serious adverse events. The reported rate of successful intercourse was significantly higher in the udenafil group, especially up to 12 hours after dosing. Based upon these data, udenafil could be a reliable treatment option in patients who are in need of a spontaneous recovery of erectile function.
Efficacy of Udenafil up to 12 Hours

and who desire sexual intercourse without concerns over the duration of efficacy of the drug.

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Conflict of Interest: None.

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(a) Final Approval of the Completed Article
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References