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Effect of food on the pharmacokinetics of the oral phosphodiesterase 5 inhibitor udenafil for the treatment of erectile dysfunction

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Udenafil is a newly marketed phosphodiesterase type 5 (PDE5) inhibitor.
- Udenafil is safe and well tolerated in healthy subjects, and effective as treatment for erectile dysfunction.
- The effect of food on the pharmacokinetics of PDE5 inhibitors varies.

WHAT THIS STUDY ADDS

- This is the first study to determine the effect of food on the pharmacokinetics of udenafil.
- Food generally does not affect the bioavailability of udenafil, although a low-fat diet shows a tendency to decreases the absorption rate of udenafil.

AIMS

Udenafil is a cyclic guanosine 3′,5′-monophosphate-specific phosphodiesterase type 5 (PDE5) inhibitor developed for the treatment of erectile dysfunction. The aim was to evaluate the effect of food on the pharmacokinetics of udenafil.

METHODS

An open, randomized, three-way crossover study was conducted. Fifteen healthy male volunteers received a single 200-mg oral dose of udenafil while fasting, after a low-fat meal, and after a high-fat meal separated by 7-day washout periods. Serial blood samples were taken up to 48 h after oral administration.

RESULTS

Under fasting conditions, udenafil was rapidly absorbed and t_{max} was observed typically 1.5 h after administration. The mean t_{max} values after a low-fat meal and a high-fat meal were 2.6 and 2.1 h, respectively. The ratios (90% confidence intervals) of the geometric means compared with the fasting condition for C_{max} and AUC_{last} were 0.79 (0.70, 0.90) and 0.96 (0.89, 1.03) in the low fat-fed condition, respectively, and 1.01 (0.89, 1.15) and 1.03 (0.96, 1.11), respectively, in the high fat-fed condition.

CONCLUSIONS

The t_{max} of udenafil was delayed under the fed conditions. However, although the C_{max} was reduced by approximately 21% in the low fat-fed state, overall bioavailability was not affected when taken with food.

Introduction

The phosphodiesterase 5 (PDE5) inhibitor maintains penile erection by inhibiting the hydrolysis of cyclic guanosine 3′,5′-monophosphate, which plays an important role in erection. Udenafil (Zydena®; Dong-A Pharmaceutical Co., Seoul, Korea) is a PDE5 inhibitor developed as a medical treatment for erectile dysfunction. Having a molecular structure similar to that of sildenafil, it has been found that udenafil is comparable to sildenafil citrate in terms of selectivity for PDE5 [1]. Previous Phase I clinical study data show that udenafil has a longer drug exposure in comparison with other drugs of similar mechanism [2, 3], since it has a time to maximum drug plasma concentration of 0.8–1.3 h, and a terminal elimination half-life of 7.3–12.1 h [4].

It has been demonstrated that food intake simultaneous with or just before drug administration can affect drug pharmacokinetics. Udenafil is likely to be taken with food, and modification of the dosing regimen may be required in the event of any subsequent significant change in the pharmacokinetics. Therefore, we examined the effect of food on the pharmacokinetics of udenafil by administering it after fasting and low-fat and high-fat meals.

Methods

Fifteen healthy male volunteers were studied as per a protocol approved by the Institutional Review Board of Seoul National University Hospital after obtaining written informed consent. The mean (SD) age of the subjects was 25.2 (4.6) years, and the mean height and weight were 174.3 (4.8) cm and 69.4 (7.9) kg, respectively.

This study was conducted in a randomized, open-label, three-treatment, three-sequence crossover design. The subjects were randomly assigned to one of three sequence groups (fasting–low-fat meal–high-fat meal, low-fat meal–high-fat meal–fasting, and high-fat meal–fasting–low-fat meal), with five subjects in each group. During each study session, subjects received a single 200-mg oral dose of udenafil within 30 min after the start of eating in the case of the low-fat or high-fat meal conditions. The caloric contents of the low-fat and high-fat meal were 600 kcal and 900 kcal, respectively, according to the recommendations of US Food and Drug Administration guidance [5] and also a domestic guideline [6]. Sixty percent of the calories in the low-fat meal were derived from carbohydrate, 20% from protein, and 20% from fat. In the high-fat meal, 30% of the calories were derived from carbohydrate, 15% from protein, and 55% from fat.

Venous blood samples (8 ml) were taken at predose (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32 and 48 h after drug administration. The udenafil concentration in plasma was determined by using liquid chromatography-tandem mass spectrometry. Intra- and interday accuracy ranged from 97.4 to 102.3%, and intra- and interday precision, expressed as the percent coefficient of variation, was <4%, providing evidence that the plasma concentration analysis method had reliability over the given range.

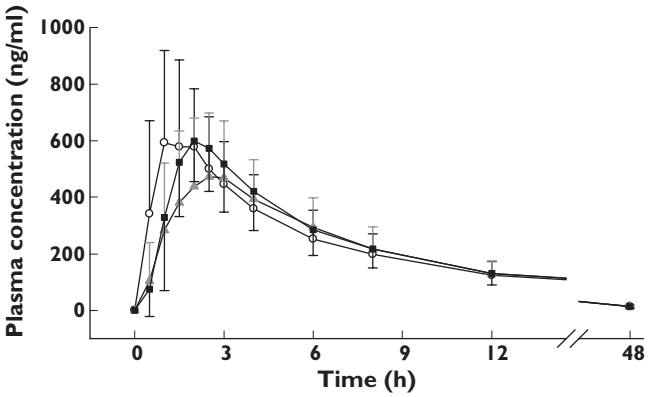

Figure 1

Mean plasma concentration–time profiles of udenafil after oral administration of udenafil 200 mg to 15 healthy male volunteers under fasting, low-fat meal and high-fat meal conditions, respectively. Bars represent standard deviations. fasting (—○—); low-fat meal (—▲—); high-fat meal (—■—)

Pharmacokinetic analysis was performed by noncompartmental evaluation using WinNonlin® (Version 5.1; Pharsight Co., Mountain View, CA, USA). Statistical analysis was performed using SPSS 12.0 (SPSS Inc., Seoul, Korea). The point estimate and 90% confidence interval (CI) [5, 7] for the geometric mean ratio of the low fat-fed state to the fasting state and the high fat-fed state to the fasting state in log transformed C_{max} and AUC_{last} were calculated by analysis of variance (ANOVA) using a mixed effects model fitting sequence, period and treatment as fixed effects and subject (sequence) as a random effect.

Results

Following the administration of udenafil under fasting conditions, C_{max} was achieved at 1.5 h after dosing, and udenafil was not detected in plasma 48 h after dosing. When udenafil was administered after food intake, t_{max} was delayed to 2.6 h after a low-fat meal and 2.1 h after a high-fat meal, but exhibited a similar elimination profile to that of the fasting state thereafter (Figure 1, Table 1).

The pharmacokinetic parameters after a low-fat and a high-fat meal were compared with those of the fasting state. The geometric mean ratio between the low fat-fed state and the fasting state was 0.79 (90% CI 0.70, 0.90) for C_{max}, and 0.96 (0.89, 1.03) for AUC_{last}, showing no remarkable difference in the extent of drug absorption, although the C_{max} did decrease by 21% on average. The geometric mean ratio between the high fat-fed and fasting state was 1.01 (0.89, 1.15) for C_{max}, and 1.03 (0.96, 1.11) for AUC_{last} (Table 1), with no apparent differences in maximum

Table 1

Mean plasma pharmacokinetic parameters of udenafil after 200-mg single oral administration under fasting, low-fat meal and high-fat meal conditions and geometric mean ratios of C_{max} and AUC_{last} between the low-fat meal and fasting and between the high-fat meal and fasting conditions

Parameter	Fasting	Low-fat meal	High-fat meal	Geometric mean ratio (90% CI) Low-fat meal/fasting	High-fat meal/fasting
C_{max} (ng ml^{-1})	702.9 ± 282.7	560.5 ± 215.1	687.5 ± 172.2	0.79 (0.70, 0.90)	1.01 (0.89, 1.15)
AUC_{last} (ng h ml^{-1})	5119.8 ± 1846.9	4919.9 ± 1562.5	5184.9 ± 1366.1	0.96 (0.89, 1.03)	1.03 (0.96, 1.11)
t_{max} (h)*	1.5 (0.5–2.5)	2.6 (1.0–4.0)	2.1 (1.0–3.0)	–	–
$t_{1/2}$ (h)	12.8 ± 1.2	12.9 ± 1.5	12.4 ± 1.3	–	–

Values represent the mean ± SD except for t_{max}. *Reported as the mean (range).

plasma drug concentrations and drug absorption between the high fat-fed and fasting states.

There were no significant differences between the treatment groups regarding adverse events, vital signs, laboratory tests, or 12-lead electrocardiograms (data not shown).

Discussion

This study was performed to examine the effect of food on the pharmacokinetics of udenafil, a PDE5 inhibitor developed for erectile dysfunction. As a high-fat diet frequently affects drug absorption, this study attempted to determine the maximum effect of food on the pharmacokinetics of udenafil by drug administration after a high-fat meal. It also evaluated the degree of alteration in the pharmacokinetics of udenafil after a low-fat meal, since a typical Asian diet has lower calories and low fat content. The differences in pharmacokinetics between fed conditions and the fasting condition were assessed by t_{max}, C_{max} and AUC.

The findings of this study suggest that food does not have a significant influence on the extent of absorption of udenafil, whereas the delay of t_{max} and reduction of C_{max} indicate a decreased drug absorption rate by food intake. In the study, the amount of reduction in the absorption rate was found to be larger after a low-fat meal than after a high-fat meal, contradicting the general belief that a high-fat diet has a greater effect on pharmacokinetics than a low-fat diet. The authors reason that this might have resulted from the lipophilicity of udenafil. In general, drugs with a high lipophilicity exhibit increased absorption when they are administered with a high-fat diet [8], which increases pancreatic and biliary secretion, resulting in an increased dissolution rate. Udenafil is lipophilic, displaying a 0.76–1.85 octanol/water partition coefficient (Log P) in approximately pH 1 to pH 7 [9]. Thus, it can be inferred that the increased solubility by the high-fat meal was responsible for the higher absorption rate of udenafil compared with the low-fat meal, although the absorption rate was decreased overall compared with the fasting state.

In this study, the geometric mean ratio for C_{max} between the low fat-fed condition and fasting condition was 0.79, with 0.70, 0.90 as the 90% CI, which was slightly outside the range of 0.80 to 1.25 that suggests absence of food effect on bioavailability, generally [5]. However, considering that the amount of reduction in C_{max} was not great and also considering that the clinical effect is thought to be more closely related to the overall exposure to the drug, rather than the concentration itself [9, 10], these findings are not expected to influence the therapeutic effect.

In conclusion, there was little difference in the overall exposure of the drug, not implying any clinical significance. Thus, udenafil can be administered without any limitation of meal conditions, and a modification of dosing regimen is considered to be unnecessary.

Competing interests

None to declare.

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