Absence of Food Effect on the Extent of Alprazolam Absorption from an Orally Disintegrating Tablet

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Study Objective. To evaluate the effect of a standardized meal on the bioavailability of alprazolam formulated as an immediate-release orally disintegrating tablet (ODT) in healthy volunteers.

Design. Single-dose, randomized, open-label, two-period crossover study.

Setting. Contract research organization clinic.

Subjects. Sixteen healthy volunteers (seven men, nine women), aged 20–50 years.

Intervention. Subjects were administered a single dose of alprazolam ODT 1.0 mg during two treatment periods—under fasting conditions and after a standard high-fat breakfast—separated by a 7-day washout period,

Measurements and Main Results. Blood samples for determination of alprazolam pharmacokinetics were collected by venipuncture up to 72 hours after dosing. A validated liquid chromatography with tandem mass spectrometry detection method was used to quantify the alprazolam plasma concentration. The overall extent of alprazolam absorption from the ODT formulation, as measured by area under the concentration-time curve, was unaffected during fed conditions. However, the rate of alprazolam absorption was slower after administration during fed relative to fasted conditions. The mean maximum observed plasma concentration (C_{max}) decreased approximately 25%, and time to C_{max} (T_{max}) was delayed approximately 1.5 hours when food was administered before dosing.

Conclusion. Coadministration of food was shown to have no effect on extent of absorption of immediate-release alprazolam ODT 1.0 mg when compared with drug administration in the fasted condition; however, the rate of drug absorption was decreased. The clinical significance of the difference in rate of alprazolam absorption is unknown but thought to be minimal.

Key Words: alprazolam, food effect, pharmacokinetics, orally disintegrating tablet.

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Alprazolam is a benzodiazepine that is structurally related to diazepam. It is indicated for anxiety and panic disorders and exhibits some antidepressant activity.[1] The oral dosage for anxiety is 0.5–4 mg/day, divided into 2–4 doses. For panic disorder, dosages range from 1–10 mg/day, divided into 3–4 doses.

After oral administration, immediate-release alprazolam is readily absorbed.[2] The peak plasma concentration (C_{max}) is reached about

1.5–2 hours after administration of an alprazolam orally disintegrating tablet (ODT) given with or without water. When taken with water, the mean time to reach C_{max} (T_{max}) occurs about 15 minutes earlier than when taken without water. No changes in C_{max} or area under the plasma concentration–time curve (AUC) occur when alprazolam ODT is administered with or without water. Plasma concentrations are proportional to the administered dose. Peak plasma concentrations of 8.0–37 ng/ml are observed over the dose range of 0.5–3.0 mg. The terminal half-life is approximately 12.5 hours in healthy adults.

When alprazolam is administered as a sustained-release tablet, a standard meal has minimal effect on the drug's rate and extent of absorption.[3] The objective of this study was to evaluate the effect of a standard meal on the bioavailability of alprazolam formulated as an immediate-release ODT in healthy volunteers.

Methods

Study Design and Subjects

This was a single-dose, randomized, open-label, two-period crossover study in healthy, nonsmoking adult subjects. Exclusion criteria were pregnancy or breastfeeding, or use of a hormonal oral or transdermal contraceptives within 30 days, use of a hormonal injectable contraceptive within 90 days, or use of a hormonal implanted contraceptive within 6 months of study initiation.

Subjects were not to consume any alcohol-containing foods or beverages for the 24 hours before or during each treatment period. In addition, subjects were not to consume citrus-, caffeine-, or xanthine-containing foods or beverages for 48 hours before or during each treatment period. Enzyme-altering agents were not allowed 30 days before study initiation. Subjects were to be nicotine and tobacco free for at least 6 months before enrolling in the study. Use of over-the-counter drugs were prohibited 7 days before study initiation and during the study. Use of prescription drugs were not allowed 14 days before or during the study.

The study was conducted at an MDS Pharma Services (Lincoln, NE) clinic in accordance with the relevant International Conference on Harmonization guidelines (Good Clinical Practices), the applicable national requirements, and the principles described in the Declaration of Helsinki. The MDS Pharma Services institutional review board approved the protocol, the informed consent form, and the Authorization for Use and Disclosure form. All subjects read and signed the informed consent form before study initiation.

Subjects reported to the clinic on the evening before each dosing day. Serum pregnancy testing in the women and urine drug screening for cannabinoids, cocaine, and alcohol in all subjects were performed. Negative results were required for enrollment and/or continuation in the trial.

All subjects received a single-dose of alprazolam ODT 1.0 mg (CIMA Labs, Inc., Eden Prairie, MN) in two treatment periods, separated by a 7-day washout period. Treatment A consisted of administering one ODT after a 10-hour overnight fast, and treatment B consisted of administering one ODT after a standard high-fat breakfast. The meal consisted of two fried eggs, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes, and 240 ml (8 fluid oz) of whole milk. This breakfast derived approximately 150, 250, and 500–600 calories from protein, carbohydrates, and fat, respectively.

Subjects were randomly assigned to receive either treatment A followed by B or treatment B followed by A. For each treatment, one alprazolam ODT was allowed to disintegrate on the subject's tongue, the drug mixture was swallowed, and 240 ml of water was administered. During treatment B, breakfast began 30 minutes before drug administration, and the drug was given no more than 5 minutes after meal completion.

Sample Collection

Blood samples (7 ml) for determination of alprazolam pharmacokinetic parameters were collected by venipuncture, with tripotassium ethylenediaminetetraacetic acid (K_3EDTA) added as an anticoagulant. Blood samples were collected during each study period before dosing (0 hr) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. Samples were collected and processed under yellow lighting per protocol instructions. Plasma was separated by centrifugation and frozen at -20°C until assayed.

Analytic Methods

A validated liquid chromatography with tandem mass spectrometry detection method was used to quantify alprazolam concentrations in human K_3EDTA plasma (MDS Pharma Services, Lincoln, NE). Briefly, 0.3-ml aliquots of plasma were supplemented with internal standard (d_5-

alprazolam) and subjected to protein precipitation with use of acetonitrile. Separation was achieved from a 20-µl aliquot of extract by using high-performance liquid chromatography on a Cyclone TurboFlow (Cohesive Technologies, Franklin, MA) high-turbulence liquid chromatography loading column (50 x 1 mm, 50 µm) and a Hypersil-Keystone BDS Hypersil (Thermo, Waltham, MA) C18 analytic column (50 x 4.6 mm, 3 µm). The mass spectrometer was operated under tandem mass spectrometry conditions, and data were acquired in the multiple reaction mode monitoring positive ions. The resultant chromatograms were integrated, and a calibration curve was constructed from the peak area ratio versus the concentration standards. A weighting of $1/x^2$ was used for curve fitting.

Validation data generated during the analytic portion of this study confirmed the precision and accuracy of the method. The calibration curve ranged from 0.100–15.000 ng/ml, and the correlation coefficients were 0.996780 or greater. The lower limit of quantification was 0.100 ng/ml. Coefficients of variation from the quality control samples were 6.73% or less. The relative errors for the calibration curve and quality control samples ranged from -4.00–6.72%.

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined by noncompartmental analysis using WinNonlin, version 4.0 (Pharsight Corp., Mountain View, CA). The C_{max} and T_{max} were obtained directly from the plasma concentration–time profile from each subject in each treatment. The AUCs from time zero to the last quantifiable sampling point (AUC_{0-t}) and from time zero extrapolated to infinity ($AUC_{0-\infty}$) after dosing were calculated by using the linear trapezoidal method. The terminal rate constant (k_{el}) was calculated by linear regression of the terminal linear portion of the log concentration versus time curve. Terminal half-life was calculated as $\ln(2)/k_{el}$. Oral clearance was calculated by dividing the oral dose by $AUC_{0-\infty}$.

Statistical Methods

Statistical analyses were performed for alprazolam pharmacokinetic parameters on all subjects who completed the study.

A parametric (normal-theory) general linear model was applied to the natural logarithmic transformation of the $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

The analysis of variance (ANOVA) model included the following factors: sequence, subject within sequence, period, and formulation. The sequence effect was tested by using the subject-within-sequence mean square, and all other main effects were tested by using the residual error (error mean square).

The two 1-sided hypotheses were tested at the 5% level for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} by constructing 90% confidence intervals (CIs) for the ratio of the fed:fasted means.[4] The 90% CI was obtained from the antilogs of the lower and upper bounds of the 90% CI for the difference in the least-squares means of the natural logarithmic–transformed data. The statistical analysis was performed by using the appropriate SAS procedure, version 6 (SAS Institute Inc., Cary, NC).

Absence of food effect was to be concluded if the corresponding 90% CI for the ratio of the geometric means of treatment with the high-fat breakfast:treatment in the fasted state was contained within the equivalence range of 80–125% for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, provided that there were no clinically relevant differences in median T_{max} values.[5]

Results

Sixteen healthy subjects (seven men, nine women) participated in the study. Mean age was 34 years (range 20–50 yrs), mean height was 68.5 inches (range 63–75 in.), and mean weight was 158 lbs (range 128–196 lbs). One subject was American Indian, one was African-American, one was European–Middle Eastern, and 13 were Caucasian. All 16 subjects completed the study.
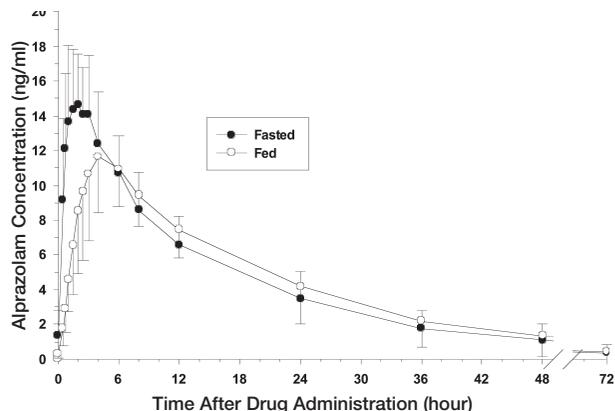

Figure 1. Plasma concentrations (mean ± SD) after oral administration of an alprazolam 1.0-mg orally disintegrating tablet under fed and fasted conditions.

Table 1. Bioavailability Data After Oral Administration of an Alprazolam 1.0-mg Orally Disintegrating Tablet Under Fed and Fasted Conditions

Pharmacokinetic Parameter	Fed Condition	Fasted Condition	90% CI (%)[a]	Mean Ratio (%)[a]
AUC_{0-t} (ng•hr/ml)	255.1 ± 100.8	247.0 ± 81.92	97.3–106.7	101.9
$AUC_{0-\infty}$ (ng•hr/ml)	268.1 ± 121.0	256.9 ± 96.13	97.7–107.4	102.5
C_{max} (ng/ml)	12.43 ± 3.11	16.13 ± 3.54	68.8–84.0	76.0
Half-life (hrs)	13.54 ± 4.30	13.08 ± 4.37	ND	ND
Cl/F (ml/hr)	4.4 ± 1.8	4.4 ± 1.7	ND	ND
T_{max} (hrs)	4.0 (2.53–6.03)	2.5 (0.75–4.01)	ND	ND

Data are mean ± SD, except for T_{max}, which is median (range).
CI = confidence interval; AUC_{0-t} = area under the plasma concentration–time curve from time zero to the last quantifiable sample point; $AUC_{0-\infty}$ = AUC from time zero extrapolated to infinity; C_{max} = maximum observed plasma concentration; Cl/F = oral clearance, where F = bioavailability; T_{max} = time to reach C_{max}; ND = not done.
[a]Determined by using logarithmic-transformed data for fed (test) versus fasted (reference) treatment.

Mean ± SD plasma alprazolam concentration-time profiles for the fed and fasted treatments are presented in Figure 1. The mean ± SD or median pharmacokinetic parameters are summarized in Table 1, as are the results of the statistical comparison between the treatments.

Results of the ANOVA of logarithmic-transformed AUC_{0-t} and $AUC_{0-\infty}$ indicated no statistically significant effects of sequence or treatment, using an α of 0.05. Effects due to period and subject nested within sequence were statistically significant; however, these effects did not have an impact on the comparison of treatments.

The ANOVA results for logarithmic-transformed C_{max} indicated a statistically significant effect due to treatment, as reflected by the 90% CI about the mean ratio. The subject-within-sequence effect was also found to be statistically significant; however, as treatment comparisons were made within subject, this result had no impact on the comparison of treatments. Effects due to sequence and period were not found to be statistically significant.

The mean ratios of logarithmic-transformed AUC_{0-t} and $AUC_{0-\infty}$ for the comparison of treatment B (fed) versus treatment A (fasted) were 101.9% and 102.5%, respectively, whereas the 90% CIs were 97.3–106.7% and 97.7–107.4%, respectively. These ranges were within the 80–125% range where these parameters were defined as bioequivalent. However, the mean ratio of logarithmic-transformed C_{max} was 76.0% and the 90% CI was 68.8–84.0%. In addition, the median T_{max} value was delayed approximately 1.5 hours during fed conditions, with a median of 4.0 hours compared with a median of 2.5 hours after fasted administration. The mean half-lives and oral clearances were similar for the fed and fasted treatments. The fraction of the AUC_{∞} that was extrapolated was less than 15% in all subjects for both treatments.

These findings indicate that the overall extent of alprazolam absorption from the ODT formulation was unaffected during fed conditions. However, the rate of alprazolam absorption was slower after administration during fed conditions. The median T_{max} increased approximately 1.5 hours when food was administered before dosing and the mean C_{max} decreased approximately 25%.

Discussion

Several studies have shown that the steady-state plasma alprazolam concentration appears to be of clinical importance.[6–8] Steady-state concentrations in the 20–40-ng/ml range minimize the severity of specific anxiety-related target symptoms, lessen the occurrence of panic attacks, and optimize overall global clinical improvement.[9]

The clinical significance of the C_{max} decrease and T_{max} increase are unknown but thought to be minimal. When alprazolam plasma concentrations of after administration of immediate-release and extended-release formulations at similar doses were compared in another study, extended-release T_{max} values ranged from 4–12 hours and immediate release T_{max} values ranged from 1–2 hours.[10] In addition, with the extended-release formulation, alprazolam's C_{max} was approximately 50% of the immediate-release formulation C_{max}. Nevertheless, immediate- and extended-release alprazolam formulations were found to be equally clinically effective in improving the Hamilton Rating Scales for

Anxiety scores, anxiety ratings, work disability measures, and panic factor. The C_{max} and T_{max} differences were less in our study when comparing fed and fasted drug administration than the C_{max} and T_{max} differences when comparing administration of immediate- and extended-release formulations in the above-mentioned study.[10]

Since neither the extent of alprazolam absorption nor its clearance were significantly affected by coadministration of food with a single dose of alprazolam immediate-release ODT, steady-state alprazolam concentrations are expected to be similar when administered with or without food. Consequently, when alprazolam immediate-release ODT is coadministered with food at steady state, a significantly different clinical effect is not expected.

Conclusion

Coadministration of food was shown to have no effect on extent of absorption of immediate-release alprazolam ODT 1.0 mg when compared with drug administration in the fasted condition, but it did decrease the mean C_{max} approximately 25% in healthy volunteers. In addition, the median T_{max} increased approximately 1.5 hours. The clinical significance of the C_{max} and T_{max} differences is unknown but thought to be minimal.

Acknowledgments

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