The Impact of Calories and Fat Content of Meals on Oral Ziprasidone Absorption: A Randomized, Open-Label, Crossover Trial

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Background: Food is known to increase the bioavailability of ziprasidone. Therefore, we evaluated the effects of meals of differing caloric and fat content on steady-state ziprasidone exposure in a stable, treated group of subjects with DSM-IV diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorder (not otherwise specified) who were already receiving oral ziprasidone as their standard therapy.

Method: Patients took ziprasidone under 6 meal conditions in randomized sequences (fasted, low calorie/low fat, low calorie/high fat, medium calorie/high fat, high calorie/low fat, and high calorie/high fat); each crossover period was separated by at least 3 days for washout of the previous meal condition. Serial blood samples were obtained over the 12 hours postdose. The study was conducted from July 27 to September 28 of 2006.

Results: Maximum ziprasidone exposures in this study were observed with high-calorie meals (1000 kcal), which were nearly twice those observed under fasting conditions. The medium-calorie meal (500 kcal) was associated with exposures similar to the high-calorie meals. Low-calorie meals (250 kcal) were associated with exposures that were approximately 60% to 90% lower than those of medium- and high-calorie meals, and approached exposures seen under fasting conditions. Fat content of the meal had no significant effect on ziprasidone absorption. The ziprasidone exposures observed with medium- and high-calorie meals had less variability than those with low-calorie meals and under fasting conditions.

Conclusions: These results confirm that ziprasidone should be taken with food and that a meal equal to or greater than 500 kcal, irrespective of fat content, is required for optimal and reproducible bioavailability of the administered dose.

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Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2 *H*-indol-2-one) is an orally active antipsychotic drug used for the monotherapy of schizophrenia[1] and bipolar disorder.[2] Following oral administration with food, peak serum ziprasidone concentrations typically occur 6 to 8 hours postdose over the therapeutic dose range of 40 to 80 mg b.i.d.[3]

Oral ziprasidone absorption is influenced by the presence of food, and the U.S. prescribing information instructs patients to take the medication with food.[4] Studies in healthy volunteers have shown that the bioavailability of ziprasidone is enhanced when it is administered in the presence of a standard U.S. Food and Drug Administration (FDA) meal.[5] Absorption is also dependent on the timing of drug administration relative to food, with reduced absorption when taken 2 hours after, rather than immediately following, food.[5]

A typical FDA standard meal consists of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz of whole milk. The meal is high in both fat (approximately 50% of total calorie

content of the meal) and calories (approximately 800–1000 kcal)[6] and is more a standardized research tool than a realistic representation of the daily diet of the patient requiring treatment with an atypical antipsychotic.

We evaluated the effects of meals of differing caloric and fat content on steady-state ziprasidone exposure in a stable, treated group of subjects with schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorder who were already receiving oral ziprasidone as their standard therapy.

METHOD

A randomized, open-label, 6-way crossover trial was conducted to estimate the effects of a range of meal conditions on steady-state serum concentrations of ziprasidone.

Subjects

Subjects included were 18 to 65 years of age, with a body mass index of 18 to 36 kg/m^2 and a total body weight > 50 kg. All patients had a history of schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorder (not otherwise specified) for which chronic antipsychotic therapy was indicated and for which they were receiving oral ziprasidone 80 mg b.i.d. as their standard therapy. All subjects had maintained a stable 80-mg b.i.d. dose level for at least 2 weeks prior to joining the trial and were required to provide informed consent.

Subjects were excluded from participation if they were experiencing an acute episode, had a clinically significant electrocardiogram (ECG) abnormality, history of cardiovascular disease, or had received an investigational drug within 4 weeks prior to the study. Other exclusions were abnormal laboratory values, positive urine drug screens, smoking > 1 pack of cigarettes per day, presence of any substance or condition known to affect drug absorption within 2 weeks of study start, and blood donation within 8 weeks of the trial.

Study Design

To assess the effects of calorie content, 3 meal sizes based on calorie count (high = 1000 kcal; medium = 500 kcal; low = 250 kcal) were examined and compared with a fasted condition. To assess the effects of fat variation, high- and low-calorie meals with both high- and low-fat content were examined (50% and 15% of total calories, respectively). While the percent content of carbohydrate in all breakfast meals varied, protein content was approximately 15% of total calories in these meals.

Subjects were randomly assigned to receive the different meals in varying order (Latin square), and each meal condition was separated by a minimum 3-day washout interval. Subjects remained on their 80-mg b.i.d. regimen throughout the study, which was conducted from July 27 to September 28 of 2006.

Meal Conditions

Subjects received 1 of 5 different breakfast meals or fasted during days of pharmacokinetic measurements. Although lunches were not controlled for calorie content, the total daily calorie intake was not to exceed 3000 kcal.

In the fasted condition, subjects were administered ziprasidone 80 mg with 240 mL of water following an overnight fast of at least 10 hours. In the fed treatment groups, subjects began the recommended meal 30 minutes prior to administration of the study medication, after an overnight fast of at least 10 hours. The meal was consumed over 25 minutes, and ziprasidone 80 mg was administered with 240 mL of water within 5 minutes of meal completion.

No food was allowed for at least 4 hours after ziprasidone administration. Water was allowed ad libitum, except for 1 hour before and after drug administration. Subjects received meals at the same time in each period of the study.

Ziprasidone Measurements and Analysis

Blood samples (5 mL) for pharmacokinetic analysis were collected prior to dosing on each treatment day, and at 1, 2, 4, 6, 8, 10, and 12 hours postdose. Samples were spun (1700 g for 10 minutes at 4°C) and the resulting serum was stored at approximately –20°C until assayed. Serum samples were assayed for ziprasidone using a validated liquid chromatography coupled to tandem-mass spectrometry (LC/MS/MS) method (Bioanalytical Systems, Inc., West Lafayette, Ind.). Serum aliquots (150 μL) were fortified with 50 μL of an internal standard solution (D_4-ziprasidone at 20 ng/mL concentration) in a 96-well plate and extracted by an automated solid-phase extraction procedure using a Tomtec Quadra 96 Model 320 (Tomtec, Hamden, Conn.). The solid phase extraction eluate was evaporated to dryness and reconstituted with 20% methanol, 0.075% formic acid in 10 mM ammonium acetate (aqueous). An aliquot of the reconstituted sample was injected into an LC/MS/MS system (Bioanalytical Systems p.m.-80 isocratic pump with an LC-26A online vacuum degasser interfaced to a Sciex API 3000 tandem quadrupole mass spectrometer with an electrospray ionization source [MDS Sciex, Concord, Ontario, Canada]) set up with a Zorbax Eclipse XDB-C8 narrow bore column (2.1 mm × 50 mm, 5 μm; Agilent Technologies, Santa Clara, Calif.) and guard column (2.1 mm × 12.5 mm, 5 μm; Agilent Technologies). The mobile phase used was 32% methanol, 68% 10 mM ammonium acetate (aqueous), 0.075% formic acid at a flow rate of 0.400 mL/min. The mass spectrometer was operated in the positive ionization mode and monitored the transition ions m/z 413.20 → 193.92 (ziprasidone) and m/z 417.30 → 194.14 (D_4-ziprasidone). Quantitation was achieved using peak area ratios of 8 calibration standards over a range of 0.500–250 ng/mL. The lower limit of quantitation for the assay during sample analysis was

0.500 ng/mL for ziprasidone. Calibration curves were constructed using the best-fit line determined by quadratic regression of the calibration data utilizing a weighting factor of 1 concentration square^{-1}. Serum samples were analyzed in 16 acceptable analytic runs for ziprasidone. The percent relative error of the quality controls used during sample analysis ranged from –2.5 to 5.5 with a percent relative standard deviation of ≤ 4.4.

Pharmacokinetic measures collected were as follows: area under the serum concentration curve (AUC) over the 12-hour dosing interval, maximum serum concentration (C_{max}), and the predose concentration measured at the end of the 12-hour dosing interval (C_{trough}). Individual serum pharmacokinetic parameters and concentration versus time data for ziprasidone were summarized and tabulated using descriptive statistics.

Safety Evaluations

Safety was assessed by laboratory evaluations, 12-lead ECG, physical examinations including vital signs, and adverse event monitoring.

Laboratory Tests

Laboratory tests performed at screening included standard hematology, blood chemistry, urinalysis, and urine drug testing.

Analysis of Pharmacokinetic Parameters

Descriptive statistics (N, arithmetic mean, median, percent coefficient of variation [%CV], standard deviation, minimum, and maximum) by each fed or fasted state were calculated.

RESULTS

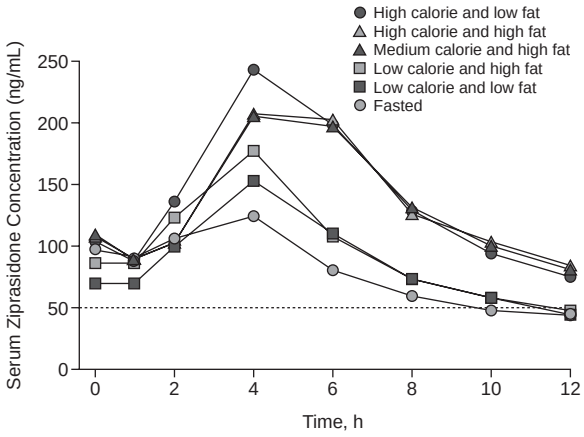
Sixteen subjects (11 men, 5 women) were assigned to study treatment, of whom 15 completed the study. One subject discontinued the study before any blood samples were collected. All pharmacokinetic data were obtained from the 15 completers.

Ziprasidone Pharmacokinetics

Consumption of food immediately prior to oral ziprasidone 80 mg administration increased ziprasidone exposure, with increases detectable in AUC, C_{max}, and C_{trough}. Figure 1 shows the arithmetic mean serum ziprasidone concentrations over time, following administration of morning ziprasidone doses to patients under various meal conditions. Clearly, there was an increase in ziprasidone C_{max} following administration with any meal relative to that in fasting subjects.

A similar pattern was observed for arithmetic means of AUC and C_{trough}. Table 1 shows AUC, C_{max}, and C_{trough} following administration of morning ziprasidone doses to patients under the various meal conditions.

Figure 1. Arithmetic Mean Serum Ziprasidone Concentrations Over Time in Patients Receiving Oral Ziprasidone Under Various Meal Conditions[a]



[a]The dotted horizontal line corresponds to the serum ziprasidone level associated with 60% brain D^2-receptor occupancy.

Although the arithmetic means of AUC, C_{max}, and C_{trough} clearly show an increase in ziprasidone AUC, C_{max}, and C_{trough} after all meals relative to that in fasting subjects, these parameters did not increase in strict proportion to the meal calorie content. Low-calorie meals (250 kcal) caused only modest increases in ziprasidone exposure relative to fasting conditions. Maximum exposures were observed with high-calorie meals (1000 kcal) and were about twice those observed under fasting conditions. Medium-calorie meals (500 kcal) were associated with bioavailability similar to that seen with high-calorie meals.

There was no clear influence of fat content on ziprasidone exposure. For any given caloric content, the AUC, C_{max}, and C_{trough} of ziprasidone were not altered by the fat content of the meal. For any given calorie content, exposure values differed by no more than 13% for low- or high-fat content of the meal (15% or 50% of total calories, respectively).

Meal calorie content affected the consistency of ziprasidone bioavailability. For example, total %CV of AUC decreased from 44% in the fasting condition to 22% to 26% with high-calorie meals. The %CV seen with low-calorie meals was similar to that of the fasting state. Medium-calorie meals were associated with variability similar to that seen with high-calorie meals. Fat content did not affect %CV.

Adverse Events

Overall, 6 subjects reported 8 adverse events (defecation urgency, diarrhea, nausea, micturition urgency, urinary incontinence, sedation, tardive dyskinesias, and lymphadenopathy) in this study, and no adverse event occurred in more than 1 subject. All adverse events were

Table 1. Arithmetic Mean (% coefficient of variation) Pharmacokinetic Parameters of Ziprasidone Given Under Various Meal Conditions (N = 15)

Parameter	A Fasted	B Low Calorie/ Low Fat	C Low Calorie/ High Fat	D Medium Calorie/ High Fat	E High Calorie/ Low Fat	F High Calorie/ High Fat
AUC, ng·h/mL	958 (44)	1070 (36)	1170 (40)	1620 (25)	1730 (26)	1650 (22)
C_{max} , ng/mL	133 (47)	158 (35)	178 (43)	238 (27)	243 (33)	247 (35)
C_{trough}, ng/mL	44.2 (48)	44.1 (40)	46.9 (38)	78.3 (33)	74.3 (31)	84.1 (37)

Abbreviations: AUC = area under the curve, C_{max} = maximum serum concentration, C_{trough} = predose concentration measured at the end of the 12-hour dosing interval.

mild in severity, except for 1 (lymphadenopathy, which was moderate in severity but considered unrelated to study medication). There was only 1 treatment-related adverse event during the study (tardive dyskinesia), and no subject had a laboratory, vital sign, or ECG result of potential clinical concern during the study.

DISCUSSION

Blockade of brain dopamine D_2 receptors is widely acknowledged to underlie the efficacy of antipsychotic drugs. Based on a number of positron emission tomography (PET) studies, a threshold of 60% D_2-receptor occupancy has been found necessary for antipsychotic response in most patients.[7] A recent PET study illustrated a strong relationship between plasma ziprasidone concentration and brain dopamine D_2-receptor and serotonin 5-HT_2–receptor occupancy,[7,8] with 60% D_2-receptor occupancy being achieved at a plasma ziprasidone concentration of 50 ng/mL. Since food influences ziprasidone absorption, and thus plasma ziprasidone levels, there is a possibility that food, or its substituents, can modify the safety and efficacy of oral ziprasidone.

This study examined which components of the meal influenced ziprasidone bioavailability and, therefore, provides a clearer understanding of that relationship than previous studies utilizing an FDA standard meal. Moreover, the meals studied may reflect more closely the kind of meals consumed by patients in clinical practice. Reference conditions (i.e., high calorie, high fat, fasting) utilized in this evaluation yielded absolute pharmacokinetic parameter values similar to those seen previously.[5]

The findings of this study are essentially 3-fold: ziprasidone exposure is dependent on the caloric value of the meal, it is independent of the fat content, and taking ziprasidone with a medium- or high-calorie meal ensures more reproducible absorption. The effects of calorie and fat content on exposure in this study were consistent, whether exposure was assessed by AUC, C_{max}, or C_{trough}. Furthermore, the administration of ziprasidone 80 mg b.i.d. with each of the 6 meal conditions was safe and well tolerated with few adverse events reported.

This study has 3 main advantages over previous studies: ziprasidone was studied in steady-state conditions rather than following acute dosing, the study was conducted in a patient group rather than in a healthy volunteer cohort, and the dose used was one that would be optimal for most patients.

The influence of calorie content on ziprasidone absorption was striking, with evidence of both threshold and ceiling effects. The low-calorie meals (250 kcal) led to ziprasidone exposures that were not higher than those obtained when ziprasidone was taken while fasting. Conversely, the medium-calorie meal (500 kcal) elicited serum ziprasidone levels that were about 80% higher than those found after fasting. A further doubling of the calorie content to 1000 kcal was associated with only an approximately 5% increase in ziprasidone exposure, suggesting that no further calorie intake is required to ensure adequate ziprasidone exposure.

Despite the fact that ziprasidone is a highly lipophilic drug, the fat content of meals had no significant effect on ziprasidone exposure. However, it should be noted that the low-fat meal still contained 5 g of fat, and no conclusions can be made about the effect of smaller amounts of fat on ziprasidone absorption. The present results support the findings of a previous study that also found that the fat content of meals was not a major influence on ziprasidone bioavailability.[9]

In addition to the increased bioavailability, another clinically important finding of the study is that medium- and high-calorie meals improve the reliability of drug exposure. Variability in serum ziprasidone levels, expressed as the %CV, was substantially reduced following medium- and high-calorie meals relative to low-calorie meals or the fasting state.

The mechanism by which food enhances ziprasidone absorption is unclear. Food can have several effects on drug absorption, with distinct influences on gastric emptying, pH, and gastrointestinal volume.[10] In the absence of additional data, we are reluctant to speculate further.

Although not explicitly investigated in the present study, the effect of food on ziprasidone bioavailability has implications for drug efficacy. In the fasting state, or following low-calorie meals, trough ziprasidone levels fall below 50 ng/mL (Figure 1), the level associated with threshold (60%) brain D_2-receptor occupancy. Therefore, this study suggests that increasing the dose of ziprasidone

in the absence of adequate caloric intake may result in suboptimal plasma ziprasidone concentrations.

Collectively, these results not only confirm that ziprasidone should be taken with food but also that a meal of at least 500 kcal, irrespective of fat content, is required for optimal and reproducible bioavailability of the administered dose.

Drug name: ziprasidone (Geodon).

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