Effects of Food on the Bioavailability of Gepirone from Extended-Release Tablets in Humans: Results of Two Open-Label Crossover Studies

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ABSTRACT

Background: The new antidepressant gepirone acts preferentially on 5-hydroxytryptamine type 1A (5-HT_{1A}) receptors and functions as a 5-HT_{1A} agonist. Placebo-controlled clinical studies have established that gepirone has a good safety profile and is effective for the treatment of depression. A previous study showed that administration of gepirone immediate release 15 minutes after a meal instead of during a fast increased the mean area under the plasma concentration–time curve (AUC) by 37%. Gepirone was reformulated into extended release (ER), which necessitated further exploration of the effects of food on bioavailability.

Objective: This article describes 2 studies of the pharmacokinetic properties of gepirone ER and 1 of its metabolites, 1(2-pyrimidinyl)-piperazine (1-PP), in healthy subjects. In study 1, we assessed the effects of food and the influence of time of food intake relative to dosing on the bioavailability of gepirone ER. The objective of study 2 was to confirm that gepirone ER has similar pharmacokinetic characteristics under fed and fasting conditions.

Methods: Two open-label, randomized, single-dose, crossover studies balanced for first-order residual effects were conducted to assess the bioavailability of gepirone from ER tablets. Healthy male subjects received a 20-mg oral dose of gepirone ER. In study 1, subjects took the gepirone ER dose after a 10-hour overnight fast or 1 hour before, 15 minutes after, or 2 hours after a standard high-fat meal. In study 2, subjects either took the gepirone ER dose after a 10-hour overnight fast and continued to fast for 4 more hours or took the gepirone ER dose 15 minutes after a standard high-fat meal.

Results: Twenty-eight men (mean [SD] age, 27.2 [6.6] years) participated in study 1, and 27 men (mean [SD] age, 31.8 [9.6] years) participated in study 2. In study 1, the mean (SD) maximum peak plasma concentration ($C_{\max}$) for gepirone ER was 69.2% higher (3.25 [1.71] vs 1.92 [0.96] ng/mL) ($P \leq 0.05$) and the AUC from time 0 to 30 hours for gepirone ER was 31.9% higher (39.3 [20.6] vs 29.8 [15.3] ng/mL·h) ($P \leq 0.05$) for the 15-minute postprandial dose than for

the fasting dose, respectively. In study 2, the mean $C_{\max}$ for gepirone was 62.0% higher (4.13 vs 2.55 ng/mL) and the mean AUC from time 0 to infinity for gepirone was 24% higher (38.71 vs 31.14 ng/mL·h) for the postprandial dose than for the fasting dose ($P < 0.05$). All reported adverse effects were mild to moderate in intensity, and most (study 1) or all (study 2) occurred during the fasting state.

Conclusions: When administered with food, the bioavailability (AUC and $C_{\max}$) of gepirone ER was greater than during the fasting state, with the greatest bioavailability seen when the drug was taken 15 minutes after eating. Based on this pharmacokinetic analysis, it may be prudent to administer gepirone ER consistently, either always with or always without food. (*Curr Ther Res Clin Exp.* 2003;64:580–598) Copyright © 2003 Excerpta Medica, Inc.

Key words: gepirone, bioavailability, 5-HT_{1A} agonist, depression, anxiety.

INTRODUCTION

The new antidepressant gepirone acts preferentially on 5-hydroxytryptamine type 1A (5-HT_{1A}) receptors^{1,2} and functions as a 5-HT_{1A} agonist.^{3–5} The antidepressant activity is thought to be related to pre- and postsynaptic 5-HT_{1A} agonism. Placebo-controlled clinical studies^{6–8} have established that gepirone has a good safety profile and is effective in the treatment of depression. The initial clinical studies of gepirone used an immediate-release (IR) formulation. Gepirone was subsequently formulated as extended release (ER), which led to increased efficacy and fewer adverse effects (AEs). Several clinical trials^{9,10} have shown that gepirone ER has antidepressant efficacy, with greater tolerability at higher doses compared with gepirone IR.

A study¹¹ using ¹⁵C-gepirone administered IV and PO demonstrated that gepirone IR has a mean absolute bioavailability of 14%. However, food may alter the rate and extent of absorption of PO-administered drugs,¹² and these effects may be important because of their possible impact on clinical response. First-pass metabolism of gepirone is extensive, with little of the parent compound excreted unchanged in the urine. The 2 major active metabolites of gepirone ER are 1-(2-pyrimidinyl)-piperazine (1-PP) and 3'-hydroxy-gepirone (3'-OH-gepirone).¹¹ 1-PP affects noradrenergic transmission, and 3'-OH-gepirone is a 5-HT_{1A} agonist like gepirone.

Food increases hepatic blood flow and decreases metabolism of compounds with high hepatic extraction ratios, such as gepirone.¹³ A previous study¹⁴ showed that administration of gepirone IR 15 minutes after a meal instead of during a fast increased the mean area under the plasma concentration–time curve (AUC) for gepirone by 37%. Reformulation of gepirone into ER necessitated further exploration of the effects of food on bioavailability. In the current article, we describe 2 studies of the pharmacokinetic properties of gepirone ER and its metabolite 1-PP in healthy subjects. In study 1, we assessed the effects of

food and the influence of time of food intake relative to dosing on the bioavailability of gepirone ER. The objective of study 2 was to confirm that gepirone ER has similar pharmacokinetic characteristics under fed and fasting conditions. In addition, after the completion of study 2, a validated analytic assay for 3'-OH-gepirone became available, and the original plasma samples from this study were analyzed for that metabolite.

SUBJECTS AND METHODS

Study Population

In study 1, 28 volunteer male subjects aged 18 to 40 years and in good health, as determined by medical history, clinical laboratory analyses, 12-lead electrocardiography, and physical examination conducted within 1 to 3 weeks before the start of the studies (screening phase), were eligible. In study 2, age (18–50 years) and body weight ($\pm 10\%$ of desirable weight for height and frame) were stipulated for participation.

Earlier studies (unpublished data, NV Organon, Oss, the Netherlands) in women did not show significant gender differences in the pharmacokinetic parameters of gepirone. However, to limit intra- and intersubject variability as much as possible, only men were included in the present studies.

Exclusion criteria for both studies included a history and/or evidence of chronic infectious disease, a history of alcohol or drug abuse, current or recent gastrointestinal disease or a history of malabsorption, and renal or hepatic disease. In study 2, additional grounds for exclusion included the following: history and/or evidence of cardiac, pulmonary obstructive, endocrine, or neurologic diseases; seizures; asthma; or hypertension. Finally, subjects also were excluded from study 2 if they had any condition requiring regular treatment with drugs, medication or drug use <1 week before gepirone ER dosing or <1 month before study initiation with any agent known to alter drug-metabolizing enzymes, ingestion of alcohol <24 hours before study initiation, receipt of an investigational drug <30 days before enrollment, positive urine screen for drugs of abuse, prior participation in a gepirone study, a history of hypersensitivity or intolerance to buspirone or a chemically related compound, significant psychiatric disease, blood donation <2 months before study initiation, or consumption of >20 cigarettes/d.

Study Design and Schedule

Both studies used an open-label, randomized, single-dose, crossover design that was balanced for first-order residual effects. The study protocols and informed consent forms were reviewed and approved by the governing institutional review board (Hazelton Laboratories America Inc., Madison, Wisconsin [study 1] and Fabre Research Clinic, Inc., Houston, Texas [study 2]) before enrollment of any subject. Written informed consent was obtained from all subjects before any study-related procedures were performed. Blood and urine samples were

obtained from all subjects for clinical laboratory analysis (hematology, standard chemistry panels, and urinalysis) during screening for drugs of abuse and before treatment with gepirone ER (usually the evening before treatment), except for the first treatment session in study 2. Subjects who met the study criteria, passed screening procedures, and provided informed consent entered the treatment phase of 1 of the 2 studies.

Treatment Phase

The treatment phase of study 1 consisted of four 30-hour sessions separated by 7-day washout periods (Figure 1). The treatment phase of study 2 consisted of two 48-hour sessions separated by a 5-day washout period (Figure 2). For each session, study subjects entered the clinical facility on the evening before study drug administration. The subjects fasted (except for water) from 10:00 PM until 8:00 AM the following day (study 1) or from 9:00 PM until 7:00 AM the following day (study 2), at which time gepirone ER was given. Randomization into each treatment arm was determined using computer-generated models. Gepirone ER was administered with 200 mL of water as a single oral dose consisting of two 10-mg tablets* (study 1) or a single 20-mg tablet† (study 2).

Study 1 was a crossover study in which the subjects were randomly assigned, using computer-generated models, to 4 groups. At each study session, subjects received gepirone ER according to the following protocol: after a 10-hour overnight fast, 1 hour before a standard high-fat meal, 15 minutes after a standard

Figure 1. Study 1 design included four 30-hour treatments as follows: treatment 1 = one 20-mg gepirone extended-release (ER) dose taken after a 10-hour overnight fast; treatment 2 = one 20-mg gepirone ER dose taken 1 hour before a standard high-fat meal; treatment 3 = one 20-mg gepirone ER dose taken 15 minutes after a standard high-fat meal; and treatment 4 = one 20-mg gepirone ER dose taken 2 hours after a standard high-fat meal.

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Figure 2. Study 2 design. ER = extended release.

high-fat meal, or 2 hours after a standard high-fat meal. Study 2 had only 2 treatment arms: after a 10-hour overnight fast, subjects either took 20 mg of gepirone ER and continued to fast for 4 more hours or took 20 mg of gepirone ER 15 minutes after a standard high-fat meal. For all treatments, subjects in both studies followed a 10- or 4-hour postdose fast (except for the treatment meal in fed subjects), but received apple juice at 11:00 AM and 3:00 PM. In both studies, fed subjects were instructed to consume the standard meal within 15 minutes. In study 1, the standard meal consisted of 2 eggs, 2 slices of toast, 1 tablespoon each of butter and jelly, 2 slices of bacon, 2 oz of hash brown potatoes, and 8 fl oz (240 mL) of whole milk. The standard meal in study 2 consisted of 1 fried egg, 1 buttered English muffin, 1 slice each of American cheese and Canadian bacon, 1 serving (2.45 oz) of hash brown potatoes, 6 fl oz (180 mL) of orange juice, and 8 fl oz (240 mL) of whole milk.

Collection of Blood Samples

In both studies, venous blood samples (7–10 mL) were collected by the medical staff into prelabeled 10-mL Vacutainer® tubes (Becton, Dickinson and Co., Franklin Lakes, New Jersey) containing potassium ethylenediaminetetraacetic acid as the anticoagulant. At each treatment session, blood samples were collected immediately before dosing (time 0) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 30 hours after gepirone ER administration. Samples were also drawn at 36 and 48 hours postdose in study 2. Immediately after collection, tubes were inverted (to ensure proper mixing with anticoagulant) and then placed on ice chips. Within 1 hour, the refrigerated samples were centrifuged (1000g at 5°C) and the plasma was separated and stored frozen (at or below –20°C) in polypropylene tubes until analysis. Quality control (QC) samples, prepared before study initiation, were stored with the study samples.

Plasma Assays and Analyses

In study 1, a sensitive and specific gas chromatograph–mass spectrometer (GCMS) was used by a laboratory technician to assay plasma samples, and in study 2 a sensitive and specific liquid chromatograph–mass spectrometer

(LCMS) was used. The GCMS method was linear from 0.1 to 25 ng/mL for gepirone ER and 1-PP, with a lower limit of detection of 0.05 ng/mL for both compounds. The validated limits of quantitation (LOQ) using the LCMS method were 0.05 to 5.0 ng/mL for gepirone ER and 0.2 to 20.0 ng/mL for 1-PP. After completion of study 2, a validated assay involving LCMS was used to analyze the original plasma samples for 3'-OH-gepirone.

In study 1, the QC standards were within 10% and 6% of their nominal values for gepirone and 1-PP, respectively. Correlation coefficients for the standard curves generated in study 1 were ≥ 0.990 .

For both studies, each analytic run consisted of a set of calibration standards, QC samples, and subject samples that were quantified using a specific standard curve generated from the calibration standards. For each subject, all of the plasma samples from all of the study treatments were analyzed in a single analytic run to keep interassay variability from increasing the intrasubject variability. To verify analyte stability and assay accuracy and precision, QC samples were assayed during each analytic run. Analysis for study 1 was performed by Bristol-Myers Squibb Co.; for study 2, it was performed by TexMS Analytical Services (Houston, Texas).

Measures of Pharmacokinetic Characteristics and Tolerability

In study 1, noncompartmental methods were used to analyze pharmacokinetic parameters.¹² Maximum peak plasma concentration ($C_{\max}$) during the dosage interval and its time of occurrence ($T_{\max}$) were recorded from observed plasma concentration data. The AUC from time 0 to 30 hours (AUC_{0-30}) was calculated using the trapezoidal method.¹⁵

$C_{\max}$ and $T_{\max}$ were also taken from measured plasma concentration data in study 2, as was the time of the last nonzero (above the lower LOQ) concentration observed during the dosage interval (C_t). In addition, terminal elimination rate constants (λ_z) were determined by least squares linear regression of the terminal (natural log-linear) portion of the concentration-time curves. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2 / \lambda_z$. The AUC from time 0 to time of C_t (AUC_{0-T}) and the AUC from time 0 to 24 hours (AUC_{0-24}) were both calculated using the linear trapezoidal method. Lastly, the AUC from time 0 to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-T} + C_t / \lambda_z$.

Although neither study was used primarily to assess tolerability, the tolerability of gepirone ER was assessed continuously throughout the inpatient portion of the study, using subject-reported AEs and results of clinical laboratory analyses, vital signs, and physical examination during the treatment phase. In study 1, the relationship between AEs related to the central nervous system and mean $C_{\max}$ and AUC_{0-30} values for gepirone ER and 1-PP also was examined.

Statistical Analysis

Statistical analysis in study 1 was performed by Bristol-Myers Squibb Co.; in study 2, by New Drug Services, Kennett Square, Pennsylvania. In both

studies, comparisons of pharmacokinetic parameters between treatments were tested in the context of an analysis of variance (ANOVA) balanced for residual effects. By balancing for first-order residual effects, each treatment is preceded equally as often by all other treatments. The sequence (ie, order of treatment) and subject-within-sequence effects were estimated using type I sum-of-squares in study 1 and type III sum-of-squares in study 2. The sequence effect was tested using subjects-within-sequence as the error term. Both studies used type III sum-of-squares to test for effects due to treatment session and treatment.

The mean $C_{\max}$ and AUC_{0-30} and median $T_{\max}$ parameters for gepirone ER and 1-PP were compared in the 4 treatment arms of study 1. If the ANOVA showed statistically significant results for treatment, treatment session, or sequence effects, then the Tukey multiple comparisons procedure was used to compare mean $C_{\max}$ and AUC_{0-30} values. Statistical significance was defined as $P \leq 0.05$. Statistical analysis was conducted on log-transformed data. Analysis of median $T_{\max}$ values was based on rank data. For study 2, the 2-sided t test was used to compare $C_{\max}$ and AUC parameters ($AUC_{0-\infty}$, AUC_{0-T} , and AUC_{0-24}) for the 2 treatment arms. To investigate the relative magnitude of the difference, the true ratios and their 90% CIs were constructed using the least square means and mean square error from the ANOVA. Statistical analysis was conducted for natural log-transformed data. Because they are discrete, median $T_{\max}$ values were compared using the nonparametric Wilcoxon rank sum test. Based on US Food and Drug Administration guidelines for bioequivalence, the acceptance range for bioequivalence was 0.8 to 1.25. SAS version 6.12 (SAS Institute Inc., Cary, North Carolina) was used for statistical analyses.

RESULTS

Subjects

A total of 28 and 27 (24 subjects and 3 alternates) healthy adult male volunteers were enrolled in study 1 and study 2, respectively. The study populations were well matched in terms of baseline body weight and height, although the mean (SD) age of subjects was lower in study 1 than in study 2 (27.2 [6.6] years vs 31.8 [9.6] years, respectively) and participants in study 1 were predominantly white (26 [92.9%] vs 14 [51.9%], respectively) (Table I).

In study 2, 1 subject failed to return for the second treatment session and was lost to follow-up. Accordingly, 1 alternate was allowed to complete the study, but the other 2 alternates were discontinued from the study after the first treatment session. Twenty-eight subjects in study 1 and 24 subjects in study 2 completed all study treatments and were included in the data set for pharmacokinetic assessment. Two subjects in study 2 had positive test results for drugs of abuse on the urine drug screen before the second treatment session but were not withdrawn from the trial because they were determined not to be habitual drug users.

Table I. Demographic and clinical characteristics of all treated subjects (N = 55) at baseline.

Characteristic	Study 1 (n = 28)	Study 2 (n = 27)
Age, y		
Mean (SD)	27.2 (6.6)	31.8 (9.6)
Range	20–40	18–49
Race, no. (%) of patients		
White	26 (92.9)	14 (51.9)
African American	1 (3.6)	7 (25.9)
Hispanic	1 (3.6)	4 (14.8)
Asian	0 (0.0)	2 (7.4)
Body weight, kg		
Mean (SD)	77.6 (7.9)	76.9 (10.4)
Range	64.0–92.3	55.0–94.5
Height, cm		
Mean (SD)	182.7 (7.1)	178.7 (7.0)
Range	168.5–196.3	160.0–190.5

Study 1: Pharmacokinetic Results

Maximum Peak Plasma Concentration

In all 4 treatment arms, plasma gepirone ER concentration increased over several hours after dosing (Figure 3). $C_{\max}$ was reached 3 to 6 hours after dosing; the concentration decreased over several hours thereafter but was detectable 30 hours after dosing for all treatments. When subjects fasted for 10 hours before and 4 hours after dosing, most of them had a single peak 6 hours after dosing, although a few subjects also had a small “shoulder” peak 3 hours after dosing. In the treatment arms involving a meal (1 hour before to 2 hours after gepirone ER administration), the plasma concentration–time curve had 2 peaks (at ~3 and 6 hours after dosing) in approximately half of the subjects. This 2-peak phenomenon was most pronounced for the dose given 15 minutes after a meal. For doses given 1 hour before to 2 hours after a meal, the plasma concentrations of gepirone ER in the 6- to 16-hour period after dosing did not drop below the values for the fasting treatment arm. Plasma concentration–time curves during this period were indicative of continued absorption. In addition, no evidence showed that higher $C_{\max}$ and AUC_{0-30} values in the 0- to 6-hour time period led to loss of continued absorption.

Analysis confirmed a statistically significant increase in bioavailability (as reflected by mean $C_{\max}$ and AUC_{0-30}) for gepirone ER if it was taken 1 hour before to 2 hours after a meal instead of during fasting ($P \leq 0.05$) (Table II). The most pronounced increase (a statistically significant increase [$P \leq 0.05$] in comparison with the other treatment arms involving meals) was associated with the dose taken 15 minutes after a high-fat meal. The mean $C_{\max}$ in that

Figure 3. Mean gepirone plasma concentration–time curves from study 1. ER = extended release.

treatment arm was 69.2% higher than that for the fasting treatment arm (3.25 [1.71] vs 1.92 [0.96] ng/mL) ($P \leq 0.05$).

Time to Maximum Peak Plasma Concentration

The median $T_{\max}$ value for gepirone ER was significantly lower when the drug was given 2 hours after breakfast compared with fasting dose ($P \leq 0.05$). However, the $T_{\max}$ values did not differ significantly among the treatment arms that included meals.

Area Under the Plasma Concentration–Time Curve from Time 0 to 30 Hours

Mean AUC_{0-30} was significantly lower for the gepirone ER dose taken during fasting than for the other treatment arms. Mean AUC_{0-30} was highest for the 15-minute postprandial dose; that value was 31.9% higher than the corresponding value for the fasting treatment arm (39.3 [20.6] vs 29.8 [15.3] ng/mL·h, respectively) ($P \leq 0.05$). The difference in mean AUC_{0-30} between the fasting treatment arm and the 15-minute and 2-hour postprandial doses was statistically significant but not as pronounced ($P \leq 0.05$) (Table II).

Table II. Pharmacokinetic parameters of gepirone extended-release (ER) formulation and its metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) for the treatment arms in study 1.

Study Drug/Parameter	Timing of Gepirone ER Administration			
	10 h After an Overnight Fast	1 h Before a High-Fat Breakfast*	15 min After a High-Fat Breakfast*	2 h After a High-Fat Breakfast*
Gepirone				
C_{max} , mean (SD), ng/mL	1.92 (0.96) [†]	2.36 (1.10)	3.25 (1.71) [‡]	2.59 (1.33)
T_{max} , median (range), h	6.0 (1.5–12)	5.0 (1.5–16)	5.5 (2.5–12)	3.0 (1.0–12) [§]
AUC_{0-30} , mean (SD), ng/mL·h	29.8 (15.3) [‡]	35.7 (19.6)	39.3 (20.6) [‡]	33.2 (14.6)
1-PP metabolite				
C_{max} , mean (SD), ng/mL	2.75 (0.93)	2.78 (1.03)	3.49 (1.06)	3.34 (1.17)
T_{max} , median (range), h	5.0 (2.5–12)	6.0 (1.5–12)	6.0 (5.0–12)	5.0 (3.0–8)
AUC_{0-30} , mean (SD), ng/mL·h	49.0 (21.5)	48.0 (17.9)	55.0 (21.6)	54.7 (23.4)

C_{max} = maximum peak plasma concentration; T_{max} = time to C_{max} ; AUC_{0-30} = area under the plasma concentration–time curve from time 0 to 30 hours.

*Breakfast was preceded by a 10-hour overnight fast.

[†] $p \leq 0.05$ for fasting dose versus administration from 1 hour before to 2 hours after breakfast.

[‡] $p \leq 0.05$ for administration 15 minutes after breakfast versus administration 1 hour before or 2 hours after breakfast.

[§] $p \leq 0.05$ for administration 2 hours after breakfast versus fasting dose.

^{||} $p \leq 0.05$ for administration 15 minutes after breakfast or 2 hours after breakfast versus fasting dose.

1-(2-Pyrimidinyl)-Piperazine Metabolite

Mean plasma concentration of 1-PP also increased gradually, generally in parallel with the gepirone plasma concentration–time curve (Figure 4). For the 15-minute postprandial dose in a few subjects, the concentration–time curve had 2 peaks (at 3 and 6 hours, corresponding to the peaks for gepirone). Otherwise, the concentration–time curves for 1-PP had only a single peak. One noteworthy outlying value (43.65 ng/mL) was found in the group of subjects who received gepirone ER 1 hour before food. Because it was clearly an outlying variable, it was not included in the final calculation of the mean plasma concentration. The mean $C_{\max}$ and AUC_{0-30} values for 1-PP were higher ($P \leq 0.05$) for the 15-minute and 2-hour postprandial gepirone ER doses than for the fasting and 1-hour preprandial gepirone ER dose. Median $T_{\max}$ values for 1-PP were similar for all treatment arms, ranging from 5 to 6 hours.

Study 1: Tolerability Results

No significant abnormalities in laboratory findings or vital signs were observed for any treatment. More AEs, including dizziness, somnolence, and nausea, were recorded for the fasting and 1-hour preprandial doses than for the 15-minute and

Figure 4. Mean 1-(2-pyrimidinyl)-piperazine (1-PP) plasma concentration–time curves from study 1. ER = extended release. *Excludes 1 outlying value.

2-hour postprandial doses. The $C_{\max}$ and AUC_{0-30} values for gepirone ER and 1-PP were lower for treatments during which AEs occurred. All AEs were mild to moderate, and none of the subjects withdrew due to AEs.

Study 2: Pharmacokinetic Results

Maximum Peak Plasma Concentration

As in study 1, the plasma concentration of gepirone ER increased gradually after dosing, with $C_{\max}$ attained at 3 to 6 hours postdose (Figure 5). The concentration declined gradually thereafter but was detectable at 48 hours postdose for both treatments. As in the previous study, most of the concentration–time curves had a single peak at 6 hours after dosing.

Results of the 2-sided t test (90% CI) analyses indicated that the bioavailability of gepirone ER increased in the presence of food. The mean $C_{\max}$ value was 62.0% higher for the postprandial dose than for the fasting dose (4.13 vs 2.55 ng/mL, respectively; $P < 0.05$) (Table III).

Time to Maximum Peak Plasma Concentration and Area Under the Curve

The median $T_{\max}$ for gepirone ER was statistically significantly shorter for the postprandial dose than for the fasting dose (2.75 vs 4.50 hours, respectively;

Figure 5. Mean gepirone plasma concentration–time curves from study 2. ER = extended release.

Table III. Pharmacokinetic parameters of gepirone and its metabolites 1-(2-pyrimidinyl)-piperazine (1-PP) and 3'-hydroxy-gepirone (3'-OH-gepirone) for the fasting and postprandial doses of gepirone extended-release (ER) in study 2.

Study Drug Parameter	Postprandial Dose*	Fasting Dose†	Fed:Fasting Ratio‡	90% CI§
Gepirone				
C _{max} , mean, ng/mL	4.13	2.55	1.62	1.38–1.90
T _{max} , median, h	2.75 [¶]	4.50	—	—
AUC _{0–∞} , mean, ng/mL·h	38.71	31.14	1.24	1.08–1.44
AUC _{0–24} , mean	33.49	24.00	1.40	1.22–1.60
AUC _{0–T} , mean	37.19	29.38	1.27	1.10–1.46
1-PP				
C _{max} , mean, ng/mL	3.21	2.80	1.15	1.05–1.26
T _{max} , median, h	5.00	3.75	—	—
AUC _{0–∞} , mean, ng/mL·h	52.77	55.39	0.95	0.83–1.09
AUC _{0–24} , mean	35.36	31.42	1.13	1.00–1.26
AUC _{0–T} , mean	39.49	37.70	1.05	0.93–1.17
3'-OH-gepirone				
C _{max} , mean, ng/mL	7.69	6.54	1.18	1.11–1.25
T _{max} , median, h	7.00	5.00	—	—
AUC _{0–∞} , mean, ng/mL·h	157.00	138.00	1.14	1.06–1.31
AUC _{0–24} , mean	116.00	97.20	1.19	1.13–1.32
AUC _{0–T} , mean	148.00	125.00	1.16	1.08–1.33

C_{max} = maximum peak plasma concentration; T_{max} = time to C_{max}; AUC_{0–∞} = area under the plasma concentration–time curve from time 0 to infinity; AUC_{0–24} = AUC from time 0 to 24 hours; AUC_{0–T} = AUC from time 0 to the time of the last nonzero concentration observed during the dosage interval.

*Dose: 20 mg of gepirone ER given 15 minutes after a high-fat meal that followed a 10-hour fast.

†Dose: 20 mg of gepirone ER given 10 hours after and 4 hours before food.

‡Value for postprandial dose divided by value for fasting dose for C_{max} or AUC. Exponent of the difference (test – reference) between natural log-transformed means.

§Upper and lower 90% CIs are for the difference between test and reference.

^{||}*P* < 0.05 versus fasting dose.

[¶]*P* = 0.005 versus fasting dose.

P = 0.005); in most subjects, the *t*_{1/2} of gepirone ER was also shorter for the postprandial dose. The mean AUC_{0–∞}, AUC_{0–24}, and AUC_{0–T} values were greater for the postprandial than for the fasting dose. For example, AUC_{0–∞} was 24.3% higher for the postprandial dose than for the fasting dose (38.71 vs 31.14 ng/mL·h, respectively; *P* < 0.05) (Table III).

1-(2-Pyrimidinyl)-Piperazine Metabolite

The mean C_{max} value for the 1-PP metabolite was higher for the postprandial dose than for the fasting dose (3.21 vs 2.80 ng/mL, respectively), but the increase was not as great as it was for gepirone ER (4.13 vs 2.55 ng/mL) (Figure 6A).

Figure 6. (A) Mean 1-(2-pyrimidinyl)-piperazine (1-PP) plasma concentration–time curves from study 2. (B) Mean 3'-hydroxy-gepirone (3'-OH-gepirone) plasma concentration–time curves from study 2. ER = extended release.

The median $T_{\max}$ for 1-PP was greater for the postprandial dose than for the fasting dose (5.00 vs 3.75 hours), although the difference was not statistically significant. The mean values for AUC_{0-24} and AUC_{0-T} were also greater for the postprandial dose than for the fasting dose, although the $AUC_{0-\infty}$ mean was slightly greater for the fasting dose (Table III).

3'-Hydroxy-Gepirone Metabolite

A similar pattern of $C_{\max}$ and AUC means emerged for the 3'-OH metabolite of gepirone ER. The postprandial dose was associated with increased plasma 3'-OH-gepirone ER concentrations and an extended formation phase in the mean plasma concentration–time curves (Figure 6B). This finding was reflected in increased mean AUC and $C_{\max}$, as well as a prolonged median $T_{\max}$ (Table III).

Study 2: Tolerability Results

As in the previous study, gepirone ER was well tolerated, and the results did not raise any safety concerns. Four subjects reported a total of 5 AEs (none severe), all of which occurred in the fasting treatment arm. One subject had a single episode of nausea and vomiting, and the other 3 subjects each reported a single episode of nausea, somnolence, or dizziness. None of the AEs required treatment, and none of the subjects withdrew from the study because of an AE. No AEs were reported in the postprandial dose treatment arm.

No treatment-related trends were apparent for any hematology or serum chemistry values, nor were any treatment-related trends observed for vital signs. None of the changes seen in the clinical laboratory values during treatment were clinically significant.

DISCUSSION

The ER formulation of gepirone was developed to decrease the frequency of dose administration and to reduce peak plasma concentrations after drug administration to increase efficacy and reduce the incidence of AEs. Because these concentrations may be related to the extent to which patients experience common AEs, such as light-headedness and nausea, the use of an ER formulation may help reduce these effects, improve tolerability, and enhance efficacy.

For many PO-administered medications, the presence of food affects pharmacokinetics. This may occur through the effects of food on gastric emptying, gastrointestinal motility, splanchnic blood flow, and gastrointestinal secretions.¹² The 2 studies presented here assessed the effects of food, as well as the timing of food intake relative to dosing, on the bioavailability of gepirone ER tablets made by different manufacturers.

Results from both studies indicate that systemic exposure ($C_{\max}$ and AUC) to gepirone ER is higher when administered with a high-fat meal rather than under fasting conditions. The time to reach $C_{\max}$ was shortened by 1 to 3 hours when gepirone ER was taken postprandially. These differences in mean AUC values between fed and fasting subjects are consistent with the findings of a study of gepirone IR¹⁴ and suggest that the amount of unchanged drug reaching systemic circulation is enhanced in the presence of food, possibly because the resultant increase in hepatic blood flow could lead to a reduction in first-pass metabolism of drugs that have a high hepatic extraction ratio, such as

gepirone.^{12,16} Another explanation may be the slowing of gastric emptying, which has been found to increase the bioavailability of sparingly soluble drugs, such as griseofulvin.

The effect of food on the bioavailability of gepirone ER is comparable to that observed with the IR formulation of the drug. The 32% higher AUC_{0-30} in study 1 and the 24% increase in $AUC_{0-\infty}$ in study 2 are similar to the 37% rise in $AUC_{0-\infty}$ reported in a previous bioavailability study¹⁴ in which subjects received gepirone IR 15 minutes after a standard meal (Table IV). This similarity suggests that the food-related increase in bioavailability is unique to the disposition of gepirone rather than attributable to the effect of food on the pharmacokinetics of the tablet formulation. The data presented provided further insight into the disposition of gepirone ER. In theory, the higher C_{max} and AUC values in fed subjects in both studies could be due to rapid release and absorption of the drug as a result of interaction with food (ie, "dose dumping"). However, analysis of the gepirone plasma concentration–time curves in study 1 found no evidence of failure of extended release and absorption in the presence of food. The plasma concentration–time curves for the 6 to 16 hours after the doses given 1 hour before to 2 hours after a meal did not fall below the curve for the fasting period dose and, in fact, were indicative of continued absorption. Moreover, there was no indication that higher C_{max} and AUC_{0-30} values in the 0- to 6-hour period led to a loss of continued absorption. Thus, the enhanced C_{max} and AUC_{0-30} values with food are not likely to be due to the dose-dumping phenomenon.

Food increases hepatic blood flow and thereby decreases the metabolism of compounds with high hepatic extraction ratios, such as gepirone ER.¹³ The earlier bioavailability study of gepirone IR¹⁴ posited that a decrease in presystemic metabolism because of the food-induced increase in hepatic blood flow might account for the increased AUC when gepirone ER is taken with food. Similarly, this mechanism may be responsible for enhanced C_{max} in the fed state.

As seen with the earlier bioavailability study of gepirone IR,¹⁴ changes in mean AUC values in the presence of food were not as pronounced for 1-PP as for the parent compound in study 2, suggesting that the formation of 1-PP from gepirone ER and its clearance from plasma are similar under fed and fasting conditions.

While neither study was designed to assess the safety of gepirone ER, no safety concerns were raised. The dose administered to healthy volunteers was well tolerated by fed and fasting subjects. Interestingly, giving gepirone ER with food appeared to reduce the incidence of AEs. Although AEs such as dizziness, nausea, and headache may have been associated with rapid absorption of gepirone (high C_{max} and short T_{max}),⁶ few of these AEs in study 1 and none in study 2 occurred in subjects who took gepirone ER 1 hour before to 2 hours

Table IV. Interstudy comparison of pharmacokinetic parameters of gepirone under fed and fasting conditions.

Study	C _{max} , ng/mL		AUC, * ng/mL·h		
	Postprandial Dose [†]	Fasting Dose [‡]	Postprandial: Fasting Ratio [§]	Postprandial Dose [†]	Postprandial: Fasting Ratio [§]
Study 1	3.25	1.92	1.69	39.30	1.32
Study 2	4.13	2.55	1.62	38.71	1.24
Tay et al ¹⁴	16.98	18.73	0.91	75.69	1.37

C_{max} = maximum peak plasma concentration; AUC = area under the plasma concentration–time curve.
*Mean AUC_{0–30} (AUC from time 0 to 30 hours) (study 1) and mean AUC_{0–∞} (AUC from time 0 to infinity) (study 2 and Tay et al¹⁴).
[†]Gepirone ER (study 1 and study 2) or gepirone immediate release (Tay et al¹⁴) taken 15 minutes after a standard meal.
[‡]Gepirone ER given during a 20-hour fast (study 1) and 10 hours into a 14-hour fast (study 2).
[§]Ratio of values for postprandial over fasting treatment.

after a meal, even though absorption was more rapid in the presence of food. In fact, the $C_{\max}$ and AUC_{0-30} values for gepirone ER and 1-PP were relatively low for the treatments that were associated with AEs. Thus, these AEs could not be explained in terms of gepirone ER or 1-PP concentrations. The duration of the fast in both studies may have contributed to the frequency of AEs.

The interpretation of the findings of the present study must be tempered by 2 factors relating to the conduct of the study. First, the protocol stated that subjects who failed a urine drug test would be excluded. Two subjects who failed drug screens continued on in the study. The intent of the exclusion criteria was to exclude drug abusers who might have compromised organ function or altered metabolism. Careful questioning of these 2 subjects revealed that they were not habitual drug abusers. Second, it was necessary to enroll alternate subjects in the study. Although this is regrettable, the effect on the outcome of the study is probably minimal (furthermore, the sample sizes in these studies were small).

CONCLUSIONS

The bioavailability of gepirone ER is greater, as measured by AUC and $C_{\max}$, when given with food, although the increase depends on the timing of the food intake. Highest bioavailability occurs when gepirone ER is taken 15 minutes after a high-fat meal; the mean AUC values increased by approximately one fourth to one third and the mean $C_{\max}$ values increased by approximately two thirds compared with the values in fasting conditions. No evidence shows failure of ER and absorption in the presence of food. Although giving gepirone ER with food led to increased systemic exposure, the incidence of AEs was lower when gepirone ER was taken with food. Based on this pharmacokinetic analysis, gepirone ER may need to be administered in a consistent manner, either always with or always without food. Further clinical study of the effects of food on gepirone ER are warranted.

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REFERENCES

1. Hamik A, Oksenberg D, Fischette C, Peroutka SJ. Analysis of tandospirone (SM-3997) interactions with neurotransmitter receptor binding sites. *Biol Psychiatry*. 1990;28:99–109.
2. Blier P, Ward NM. Is there a role for 5HT_{1A} agonists in the treatment of depression? *Biol Psychiatry*. 2003;53:193–203.
3. Andrade R, Nicoll RA. Novel anxiolytics discriminate between postsynaptic serotonin receptors mediating different physiological responses on single neurons of the rat hippocampus. *Naunyn Schmiedeberg's Arch Pharmacol*. 1987;336:5–10.

4. Blier P, de Montigny C. Modification of 5-HT neuron properties by sustained administration of the 5-HT_{1A} agonist gepirone: Electrophysiological studies in the rat brain. *Synapse*. 1987;1:470–480.
5. Eison AS. Azapirones: History of development. *J Clin Psychopharmacol*. 1990;10(Suppl 3):2S–5S.
6. Jenkins SW, Robinson DS, Fabre LF Jr, et al. Gepirone in the treatment of major depression. *J Clin Psychopharmacol*. 1990;10(Suppl 3):77S–85S.
7. McGrath PJ, Stewart JW, Quitkin FM, et al. Gepirone treatment of atypical depression: Preliminary evidence of serotonergic involvement. *J Clin Psychopharmacol*. 1994;14:347–352.
8. Feiger AD, Heiser JF, Shrivastava RK, et al. Gepirone extended-release: New evidence for efficacy in the treatment of major depressive disorder. *J Clin Psychiatry*. 2003;64:243–249.
9. Feiger AD. A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. *Psychopharmacol Bull*. 1996;32:659–665.
10. Wilcox CS, Ferguson JM, Dale JL, Heiser JF. A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients. *Psychopharmacol Bull*. 1996;32:335–342.
11. Tay LK, Farnen RH, Pittman KA. Pharmacokinetics (PH) and disposition of gepirone (GEP) and 1-pyrimidinylpiperazine (1-PP) in humans after intravenous (i.v.) and oral (p.o.) administration of ¹⁴C-gepirone. *Pharm Res*. 1990;7(Suppl 9):S208. Abstract.
12. Welling PG. Effects of food on drug absorption. *Pharmacol Ther*. 1989;43:425–441.
13. Olanoff LS, Walle T, Cowart TD, et al. Food effects on propranolol systemic and oral clearance: Support for a blood flow hypothesis. *Clin Pharmacol Ther*. 1986;40:408–414.
14. Tay LK, Sciacca MA, Sostrin MB, et al. Effect of food on the bioavailability of gepirone in humans. *J Clin Pharmacol*. 1993;33:631–635.
15. Gibaldi M, Perrier D. Noncompartmental analysis based on statistical moment theory. *Pharmacokinetics*. 2nd ed. New York, NY: Marcel Dekker; 1982:409–417.
16. Melander A, Lalka D, McLean A. Influence of food on the presystemic metabolism of drugs. *Pharmacol Ther*. 1988;38:253–267.

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