

Food Interaction and Steady-State Pharmacokinetics of Itraconazole Capsules in Healthy Male Volunteers

JOSEPH A. BARONE,^{1*} JULIA G. KOH,¹ ROBERT H. BIERMAN,² JOHN L. COLAIZZI,¹
KEITH A. SWANSON,¹ MARIA C. GAFFAR,³ BRUCE L. MOSKOVITZ,³
WITOLD MECHLINSKI,³ AND VERA VAN DE VELDE⁴

College of Pharmacy, Rutgers—The State University of New Jersey, P.O. Box 789, Piscataway, New Jersey 08855-0789¹; Hurtado Student Health Center, Rutgers—The State University of New Jersey, New Brunswick, New Jersey 08903²; Janssen Research Foundation, Titusville, New Jersey 08560³; and Janssen Research Foundation, Beerse, Belgium⁴

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The influence of food on itraconazole pharmacokinetics was evaluated for 27 healthy male volunteers in a single-dose (200 mg) crossover study with capsules containing itraconazole-coated sugar spheres. This study was followed by a study of the steady-state pharmacokinetics for the same subjects with 15 days of administration of itraconazole at 200 mg every 12 h. Concentrations of itraconazole and hydroxyitraconazole, the active main metabolite, were measured in plasma by high-performance liquid chromatography. The results of the food interaction segment showed that a meal significantly enhances the amount of itraconazole absorbed. The mean maximum concentration in plasma of unmetabolized itraconazole after fasting (140 ng/ml) was about 59% that after the standard meal (239 ng/ml). The rate of elimination was not affected (terminal half-life, approximately 21 h). The mean maximum concentration in plasma of hydroxyitraconazole after fasting was about 72% the postmeal concentration (287 and 397 ng/ml, respectively). The terminal half-life of hydroxyitraconazole was approximately 12 h. Steady-state concentrations of itraconazole and hydroxyitraconazole were reached after 14 or 15 days of daily dosing. The average steady-state concentrations were approximately 1,900 ng/ml for itraconazole and 3,200 ng/ml for hydroxyitraconazole. The shape of the elimination curve for itraconazole after the last dose was indicative of saturable elimination. This conclusion was confirmed by the sevenfold increase in the area under the curve from 0 to 12 h at steady state compared with the area under the curve from 0 h to infinity after a single dose. It was furthermore confirmed by the larger-than-expected number of half-lives required to achieve steady-state plasma drug levels.

Itraconazole is a broad-spectrum antifungal compound that, like other azole antifungal agents, selectively disrupts cytochrome P-450-mediated sterol synthesis in fungal membranes, thereby leading to cell death (1). It has been studied extensively for a variety of dermatomycoses, vaginal candidiasis, and systemic mycoses, such as histoplasmosis, blastomycosis, and aspergillosis, as well as for the prophylaxis of fungal infections in immunocompromised patients (2, 5, 10). Currently, doses of 200 mg daily and 200 mg twice daily are used therapeutically.

Experiments with small numbers of subjects indicated that the extent of itraconazole absorption from solid-dose forms is enhanced by administration with food (11). In that study, polyethylene glycol-formulated capsules were used, but the currently marketed formulation of itraconazole is capsules containing itraconazole-coated sugar spheres.

The present study was undertaken with a large number of subjects to assess the effects of food on itraconazole bioavailability by use of capsules containing itraconazole-coated sugar spheres, the currently marketed formulation. A second objective of this study was to analyze the steady-state pharmacokinetics of itraconazole at 200 mg every 12 h for 15 days by use of the coated-pellet formulation. Because a major metabolite of itraconazole, hydroxyitraconazole, has antifungal activity similar to that of the parent compound under *in vitro* conditions (3, 8, 12), a third objective of this

study was to document the pharmacokinetic profile of hydroxyitraconazole.

MATERIALS AND METHODS

Subjects. Twenty-eight healthy male nonsmoking volunteers signed written informed consent statements and were enrolled following institutional review board approval. Their weights averaged 70.9 kg (range, 56.8 to 89.5) and were within 10% of normal weights for their ages, on the basis of the Metropolitan Life Insurance Company Table of Desirable Weights for Adults. Their ages averaged 23 years (range, 20 to 32). None of the subjects had any significant medical history (including gastrointestinal diseases or achlorhydria), clinically significant abnormalities, as determined by physical examination, or history of drug abuse. Pretreatment laboratory studies included hematological tests (hematocrit, hemoglobin, and complete blood count with differential), 20 biochemical tests, urinalysis, and a urine drug screen (amphetamines, barbiturates, benzodiazepine, cannabinoids, cocaine, methaqualone, opiates, and phencyclidine). Anyone participating in an investigational study or using any investigational drug within 1 month prior to starting this study was excluded. Also, subjects with a significant concurrent illness, unable to swallow capsules, or with a history of hypersensitivity to imidazole or azole compounds were not included.

Study design and procedure. The first segment of the study was a single-dose, crossover comparison of dosing after a standard breakfast versus after fasting. Each subject was

* Corresponding author.

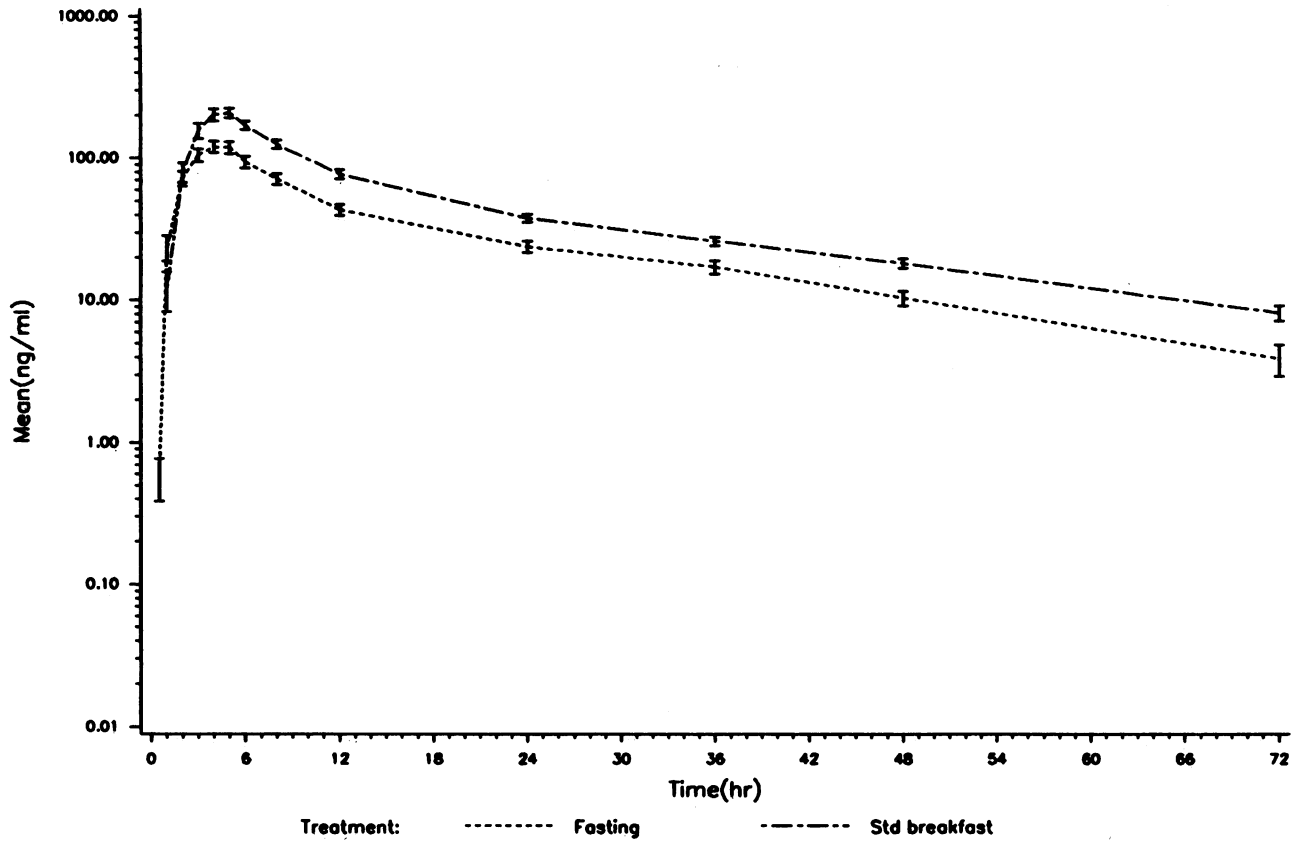


FIG. 1. Levels (mean \pm standard error) in plasma of itraconazole versus scheduled time following a single 200-mg oral dose taken after fasting or after a standard (Std) breakfast.

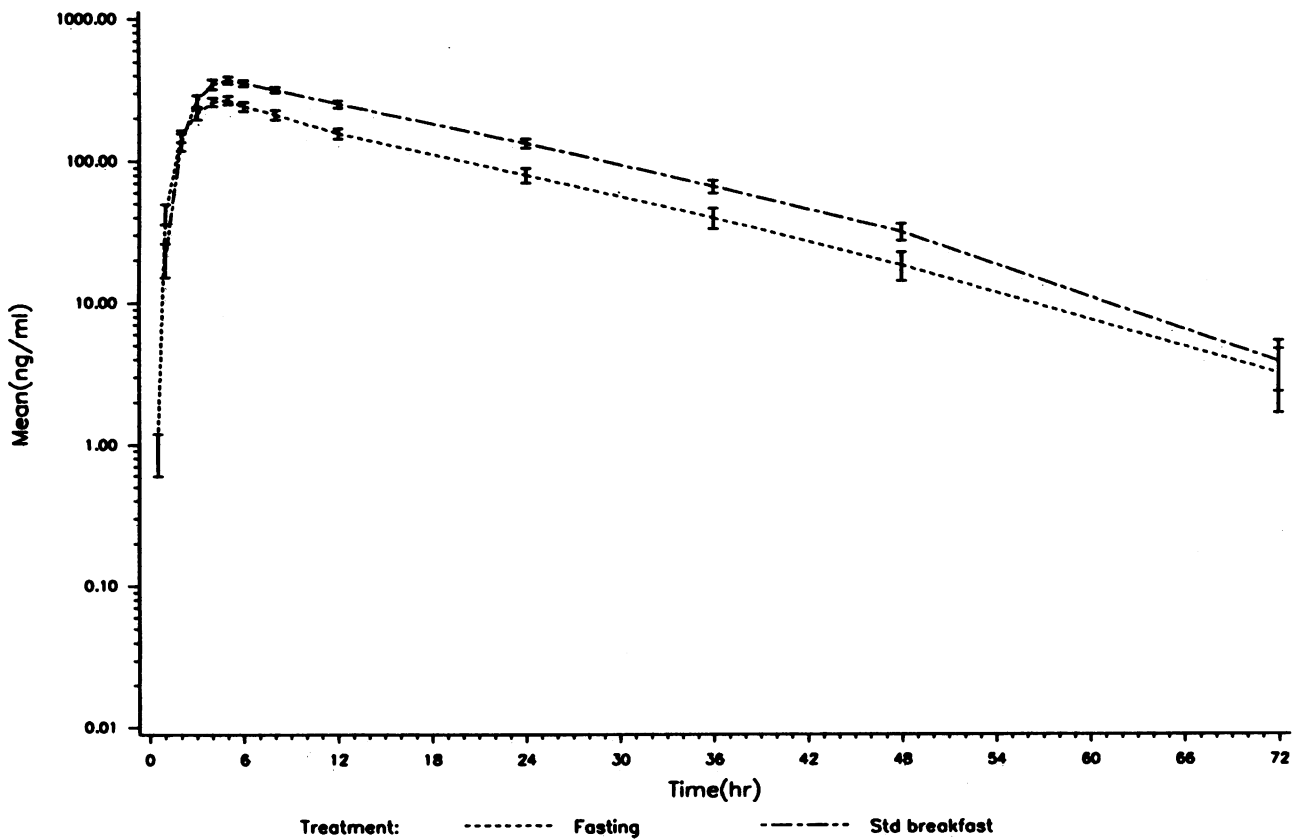


FIG. 2. Levels (mean \pm standard error) in plasma of hydroxyitraconazole versus scheduled time following a single 200-mg oral dose taken after fasting or after a standard (Std) breakfast.

TABLE 1. Pharmacokinetic parameters of itraconazole (I) and hydroxyitraconazole (H) and results of the statistical analyses for the food interaction segment

Parameter	AUC ₀₋₇₂ (ng · h/ml)		AUC _{0-∞} (ng · h/ml)		C _{max} (ng/ml)		T _{max} (h)		Terminal half-life (h)	
	I	H	I	H	I	H	I	H	I	H
Reference treatment (standard breakfast) ^a	3,124 ± 1,046	7,737 ± 2,537	3,415 ± 1,153	7,952 ± 2,648	239 ± 85	397 ± 103	4.5 ± 1.1	5.1 ± 1.6	20.6 ± 5.4	11.9 ± 3.0
Test treatment (fasting) ^a	1,883 ± 820	5,043 ± 2,366	2,094 ± 905	5,194 ± 2,489	140 ± 65	287 ± 101	3.9 ± 1.0	4.5 ± 1.1	20.9 ± 7.2	11.5 ± 3.0
Analysis of variance										
<i>P</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.047	0.082	0.87	0.50
Power	0.66	0.71	0.63	0.69	0.65	0.92	0.87	0.78	0.66	0.99
% Relative bioavailability (test/reference)	60.3	65.2	61.3	65.3	58.8	72.4	87.0	87.3	101.4	97.0
90% Confidence interval	46.4-72.4	52.0-78.3	47.0-75.6	52.0-78.6	44.8-72.7	62.7-82.1	76.3-97.6	75.3-99.3	87.6-115.1	89.6-104.4

^a Data are reported as means ± SDs.

randomized to a treatment sequence, (i) breakfast then fasting and (ii) fasting then breakfast, as determined by an SAS version 5.16-generated randomization code.

Subjects were admitted to the study site the evening prior to dosing and were fed dinner. Following dinner, no additional food intake was allowed until the fast was broken as per protocol. Subjects assigned to receive the drug with food were given the drug immediately after a standard breakfast, which consisted of orange juice, egg, bacon, toast with butter and jam, whole milk, and fresh banana. Two 100-mg itraconazole capsules were administered as a single dose with 200 ml of water. No beverage was allowed for 2 h after dosing, and no food was allowed for 4 h. Ten-milliliter blood samples were collected in heparinized tubes immediately predose (time zero) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, and 72 h postdose. The subjects remained at the study site through the 24-h blood sampling and returned for subsequent sampling. After a 2-week washout interval, subjects who had taken itraconazole after fasting were crossed over to take the capsules after a standard meal, and vice versa, and the procedure was repeated.

The drug-food interaction segment of the study was followed by a multiple-dose segment. Starting after the 72-h blood sampling at the end of the second phase of the food interaction segment, each subject was administered two 100-mg itraconazole capsules every 12 h for 14 days. All doses were taken with 200 ml of water following a meal at the study site. During this segment, trough blood samples were obtained prior to morning doses on days 4, 7, 10, 13, and 14. On the evening of day 14, the subjects were admitted to the study site and were fed dinner. A single 200-mg dose was given on the morning of day 15 after breakfast. On day 15, samples were taken predose (time zero) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96 (4 days), 168 (7 days), 240 (10 days), and 360 (15 days) h postdose. The subjects were allowed to leave the study site after the 24-h blood sampling and returned for subsequent blood sampling.

HPLC. Each blood sample was centrifuged within 1 h after sampling. Plasma was separated and stored at $\leq -20^{\circ}\text{C}$. The frozen plasma samples were sent to Janssen Research Foundation, where they were analyzed by reverse-phase high-performance liquid chromatography (HPLC) for concentrations of itraconazole (detection limit, 5 ng/ml) and its active main metabolite, hydroxyitraconazole (detection limit, 10 ng/ml). The HPLC method was based in principle on the method of Woestenborghs et al. (13), except for the addition of hydroxyitraconazole as the second standard and an increase in the polarity of the extraction solvent. The accuracy and linearity of the method were comparable to those of the previous method.

Pharmacokinetic analysis. (i) **First segment: food interaction (single dose).** The peak concentration in plasma (C_{max}) and the time to C_{max} (T_{max}) were determined by visual inspection of the individual plasma drug concentration-time data. The area under the plasma drug concentration-time curve from 0 to 72 h (AUC₀₋₇₂) was obtained via trapezoidal summation. The terminal half-life was calculated as $\ln 2/\beta$; elimination rate constant β was obtained by linear regression analysis of the terminal points of the natural log-linear plasma drug concentration-time curves. The area under the plasma drug concentration-time curve from 0 h to infinity (AUC_{0-∞}) was calculated via trapezoidal summation until the last measurable concentration in plasma and extrapolated to infinity by addition of the last measurable concentration divided by β .

(ii) **Second segment: last dose of the steady state.** C_{max} and

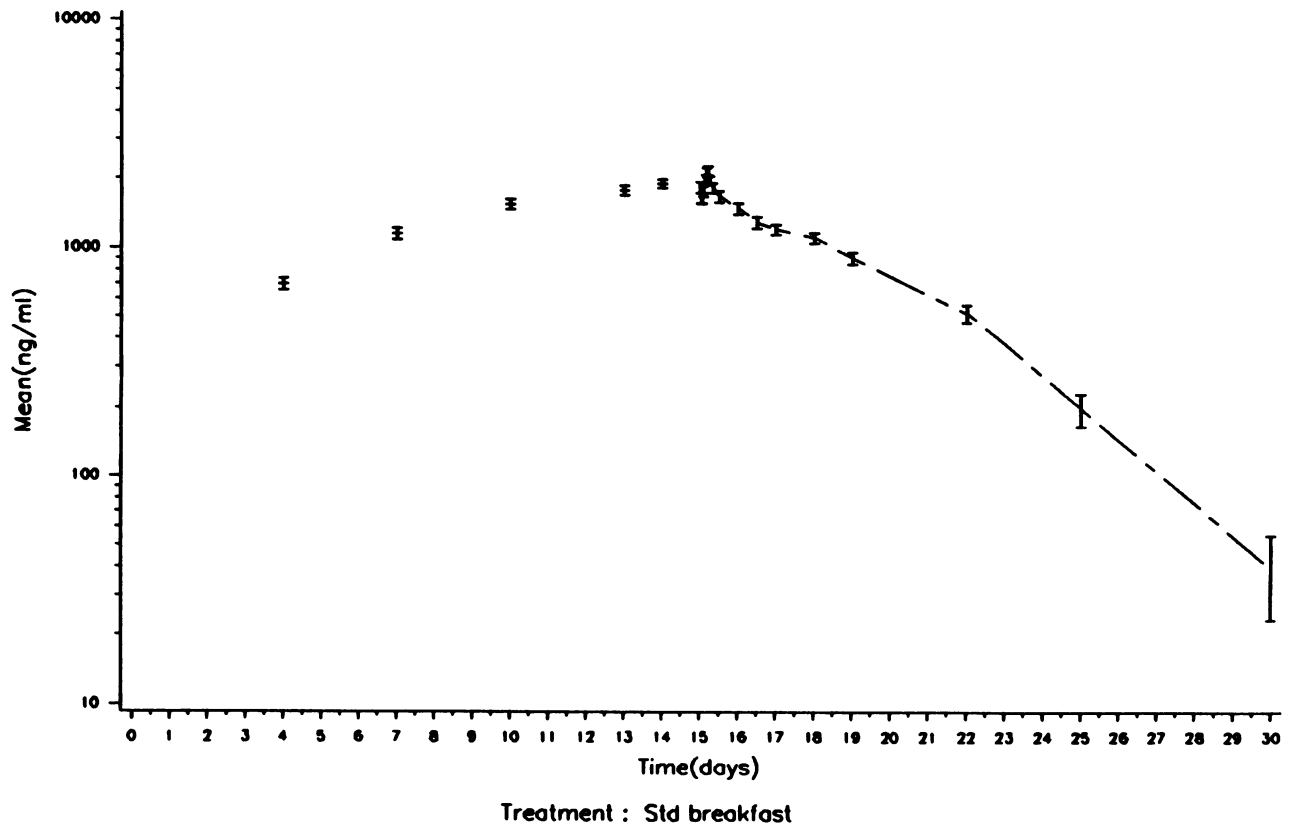


FIG. 3. Levels in plasma (mean \pm standard error) of itraconazole during 14 days of administration of a 200-mg oral dose every 12 h (steady-state segment). Std, standard.

T_{max} were determined as described above. The area under the curve of a dosing interval (AUC_{0-12}) was obtained via trapezoidal summation. The average concentration in plasma was obtained as $AUC_{0-12}/12$. The elimination kinetics for itraconazole after the last dose were analyzed by Michaelis-Menten kinetics. The rate of decrease in the concentration in plasma subsequent to equilibration of the drug in the body was calculated as $dc/dt = V_{max}c/(K_m + c)$, where V_{max} is the maximal rate of decrease in the concentration in plasma and K_m is the concentration at which the rate of decrease is one-half the maximal rate. V_{max}/K_m is the apparent first-order rate constant for terminal first-order elimination when levels in plasma are much lower than the K_m .

Estimates of the V_{max} and K_m of itraconazole were obtained by regression methods with pairs of concentrations in plasma at their respective times in the elimination phase after the last dose, as described by Garrett and Roth (4).

Statistical analysis. SAS version 5.16 was used for all data manipulation and statistical analyses. The sequences were comparable for age, race, weight, height, blood pressure, pulse, and respiration, as determined by a one-way analysis of variance for continuous variables and the chi-square test for categorical variables. The pharmacokinetic data from the food interaction segment were analyzed by use of an analysis-of-variance model appropriate for the two-period, two-treatment crossover design (6). The model included effects due to sequences, subjects within sequences, phase, and drug. For C_{max} , AUC_{0-72} , and $AUC_{0-\infty}$, analyses were repeated after the data were transformed by use of natural

logs. Type III sums of squares were used, and all tests were two sided. The posterior power of the test of drug effects was based on the detection of a 20% or greater difference between the test mean (after fasting) and the reference mean (after a standard breakfast) with testing at $\alpha = 0.05$ (two tailed).

For determination of the bioequivalence of itraconazole capsules taken after fasting or after a standard breakfast, 90% confidence intervals were computed for the bioavailability parameters by use of least-squares means. The 90% confidence intervals were operationally equivalent to the two one-sided tests approach proposed by Shiurman (9). If the 90% confidence interval for the test treatment fell completely within 80 to 120% that for the reference treatment, the two dosing conditions were declared bioequivalent with respect to the parameter tested.

For determination of whether a steady state occurred, the mean trough plasma drug concentrations on days 13, 14, and 15 were compared. A multivariate analysis of variance was used, with differences between the values on adjacent days as the dependent variables and only the intercept as the independent variable. This analysis was followed by a similar test repeated on each pair of adjacent days.

Adverse experiences. Adverse experiences were monitored by means of nondirected interviews prior to each dose and at 4, 12, 24, and 72 h after each dose during the food interaction crossover segment; prior to the blood samplings on days 4, 7, 10, 13, 14, and 15 during the steady-state segment; and after the 96 (day 4)- and 240 (day 10)-h samplings following the final dose on day 15 of the steady-state segment.

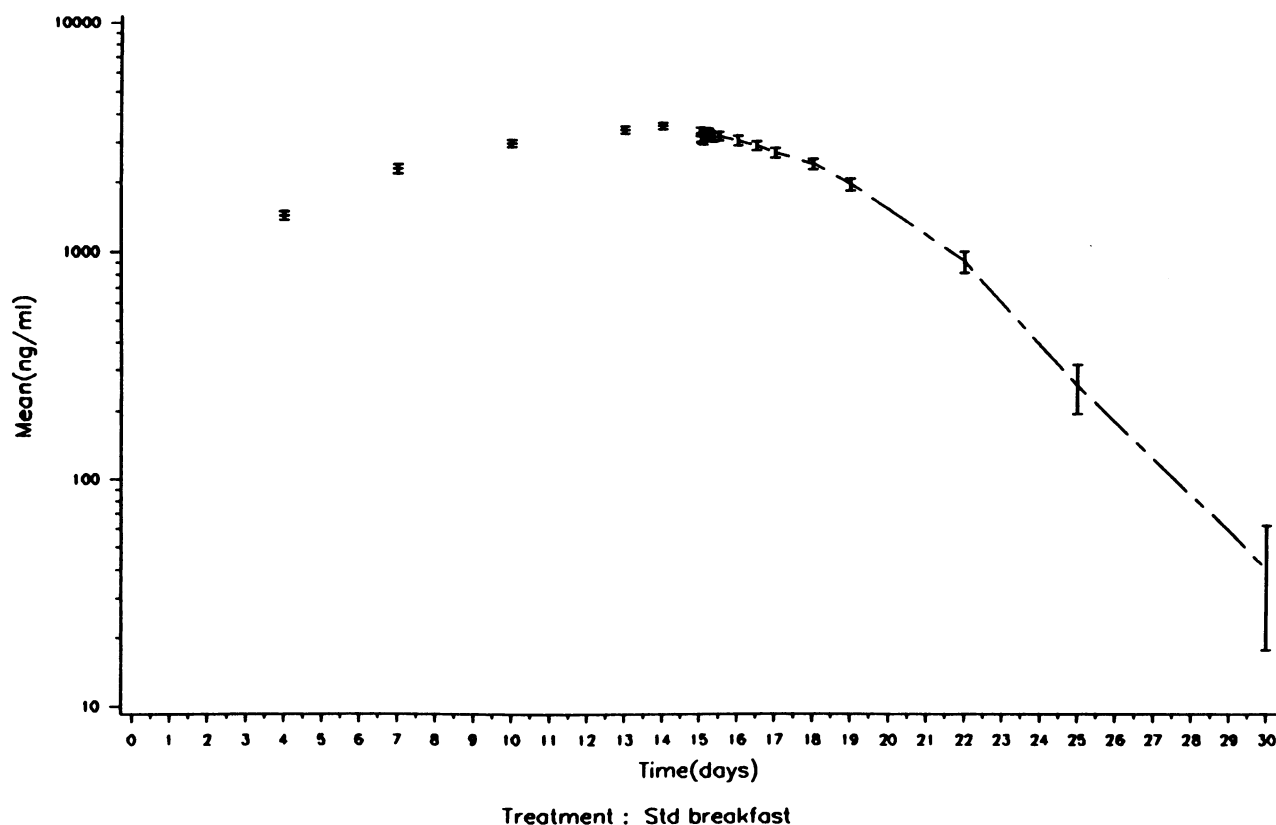


FIG. 4. Levels in plasma (mean \pm standard error) of hydroxyitraconazole during 14 days of administration of a 200-mg oral dose every 12 h (steady-state segment). Std, standard.

RESULTS

All subjects completed the study except one, who was withdrawn after phase 1 of the food interaction segment because the baseline urine drug profile proved positive. None of the data for this subject were included in the analysis. One subject experienced flatulence and two subjects experienced rash during the food interaction segment.

Food interaction pharmacokinetics. The plasma drug concentration-time curves are shown in Fig. 1 for itraconazole and Fig. 2 for hydroxyitraconazole. Table 1 summarizes the pharmacokinetic parameters and results of the statistical analyses for the food interaction segment (fasting versus fed). The reference treatment was dosing after a standard breakfast. Since the results for the \log_e -transformed data and the untransformed data were similar, only the results for the untransformed data are presented.

For both unchanged itraconazole and the metabolite hydroxyitraconazole, dosing after a meal produced higher levels in plasma than dosing after fasting, so that the two treatments were not bioequivalent with regard to AUC_{0-72} , $AUC_{0-\infty}$, and C_{max} (Table 1). The mean peak concentration in plasma of itraconazole for postfast dosing was about 59% that for postmeal dosing (140 versus 239 ng/ml). For hydroxyitraconazole, the proportion was 72% (287 versus 397 ng/ml). The $AUC_{0-\infty}$ of itraconazole for postfast dosing was about 61% that for postmeal dosing. The $AUC_{0-\infty}$ of hydroxyitraconazole for postfast dosing was on average 65% that for postmeal dosing. The differences in T_{max} were at the borderline of statistical significance (Table 1) but were of no clinical relevance. For both the parent compound and the metabo-

lite, the terminal half-life did not differ between treatments: 20.9 h (postfast) and 20.6 h (postmeal) for itraconazole and 11.5 h (postfast) and 11.9 h (postmeal) for hydroxyitraconazole.

Steady-state pharmacokinetics. Figures 3 and 4 display the time courses of the mean concentrations in plasma of itraconazole and hydroxyitraconazole, respectively. An example of the experimental concentrations in plasma of itraconazole and the fitted elimination curve in the postdistribution phase, determined by use of the Michaelis-Menten parameters V_{max} and K_m , is given in Fig. 5. A comparison of the trough concentrations in plasma at days 13, 14, and 15 is given in Table 2. The pharmacokinetic parameters of itraconazole and hydroxyitraconazole after the last dose are summarized in Table 3.

Trough concentrations in plasma of itraconazole did not further increase between day 14 and day 15 (Fig. 3 and Table 2), a result indicating that a steady state was attained at day 14. A steady state for hydroxyitraconazole was attained at day 14 (Fig. 4 and Table 2). Average steady-state concentrations in plasma were $1,881 \pm 448$ ng/ml for itraconazole and $3,214 \pm 704$ ng/ml for hydroxyitraconazole. The ratios of the AUC_{0-12} at steady state to the $AUC_{0-\infty}$ after a single dose were 7.3 ± 2.7 for itraconazole and 5.4 ± 2.0 for hydroxyitraconazole.

The elimination of itraconazole at steady state was well characterized by Michaelis-Menten kinetics (Fig. 5). The maximal rate of decrease in levels in plasma (V_{max}) was 9.34 ± 3.59 ng \cdot h/ml. The concentration at which the rate of decrease was one-half the maximal rate (K_m) was 329 ± 206

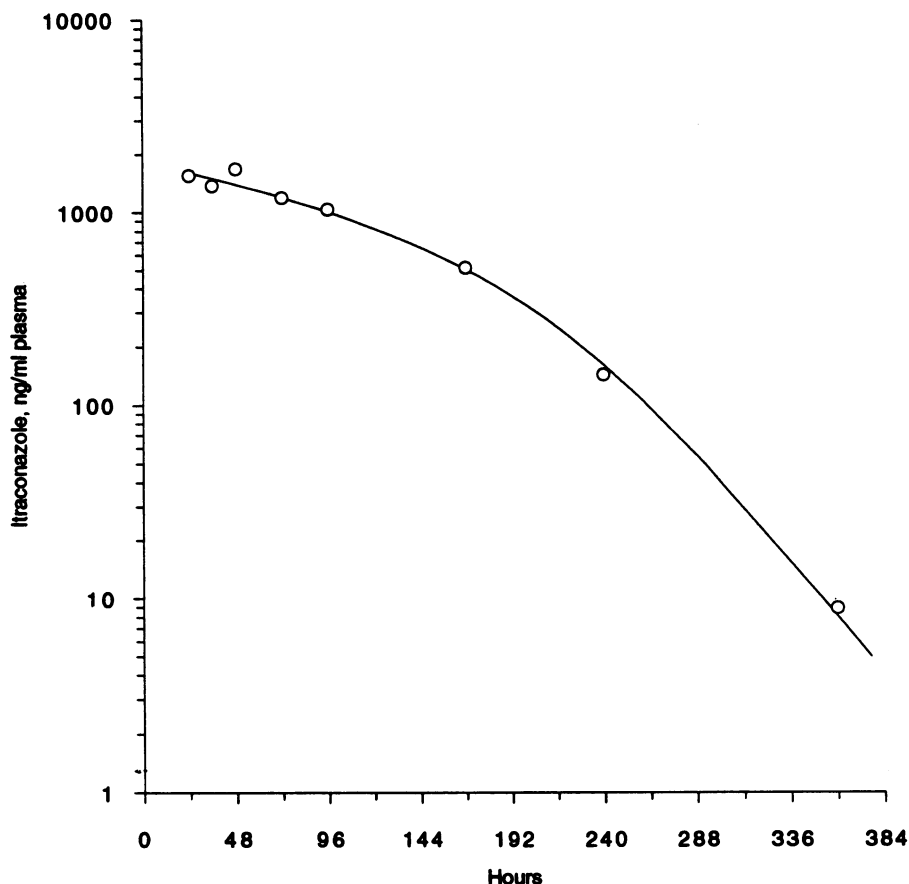


FIG. 5. Example of the experimental concentrations in plasma of itraconazole and the fitted elimination curve, determined by use of the Michaelis-Menten parameters V_{max} and K_m (subject 106).

ng · h/ml. The apparent first-order half-life at levels in plasma below the K_m was 24 ± 12 h.

DISCUSSION

The results of the food interaction segment of this study show that the administration of the currently marketed itraconazole capsule formulation after a meal enhances its absorption into the bloodstream. In the study by Van Peer et al. (11), the bioavailability of polyethylene glycol-formulated itraconazole capsules taken in the fasting state was on the order of 40% relative to the bioavailability after intake with food. The present study, in which the currently marketed pellet formulation and a larger study population were used, demonstrated absorption after fasting to be about 60% that after a meal. No substantial difference in the rate of absorption was found in either study; only the amount of drug

absorbed was affected. Itraconazole is very lipophilic and is almost insoluble in water. The presence of food may increase the solubility of itraconazole, thereby increasing its systemic absorption. Although the decrease in peak levels in plasma under fasting conditions was smaller for hydroxyitraconazole than for itraconazole, the mean hydroxyitraconazole/itraconazole AUC ratios were similar under fasting and fed conditions (i.e., 2.3 and 2.5, respectively). Thus, the extent of hydroxyitraconazole formation was not affected by the presence of food.

In general, the single-dose and steady-state concentrations in plasma obtained in our study are in accord with the values reported by Hardin et al. after the same dosage regimen with five healthy male subjects (7). The steady state of itraconazole was reached after 14 days of dosing in our study, in agreement with the 13 days observed by Hardin et al. (7). This length of time is longer than the theoretical 4 to 5 days

TABLE 2. Trough concentrations in plasma of itraconazole and hydroxyitraconazole following a standard breakfast ($n = 27$)

Drug	Concn (ng/ml) ^a in plasma on day:			Overall P value	Pairwise P value for:	
	13	14	15		Day 13 vs day 14	Day 14 vs day 15
Itraconazole	1,795 ± 450	1,922 ± 428	1,855 ± 535	0.09	0.03	0.32
Hydroxyitraconazole	3,419 ± 672	3,562 ± 662	3,349 ± 761	0.03	0.02	0.03

^a Data are reported as means ± SDs.

TABLE 3. Pharmacokinetic parameters of itraconazole (I) and hydroxyitraconazole (H) after the last dose^a

Drug	AUC ₀₋₁₂ ($\mu\text{g} \cdot \text{h/ml}$)	Avg concn (ng/ml)	C _{max} (ng/ml)	T _{max} (h)	V _{max} (ng · h/ml)	K _m (ng · h/ml)	Terminal half-life (h) ^b
I	22.6 ± 5.4	1,881 ± 448	2,282 ± 514	4.6 ± 1.8	9.54 ± 3.59	329 ± 206	24.0 ± 11.9
H	38.6 ± 8.5	3,214 ± 704	3,488 ± 742	3.4 ± 3.4			

^a Data are reported as means ± SDs.

^b Calculated as $\ln 2/(V_{\max}/K_m)$.

(four to five half-lives), assuming linear kinetics, and is an anticipated consequence of Michaelis-Menten pharmacokinetics. The higher-than-proportional accumulation of itraconazole during repeated dosing is also demonstrated by the ratio of the AUC for a dosing interval at steady state to the AUC_{0-∞} after a single dose. Assuming linear kinetics, this ratio should equal 1 but was nearly 7 in our study. From the data presented by Hardin et al., a fivefold increase can be calculated (7).

Hardin et al. reported a terminal half-life of 42 h at the end of 200-mg twice-daily dosing (7). However, in their study, concentrations in plasma were only measured over 72 h posttreatment. In our study, concentrations in plasma were measured up to 15 days after the last itraconazole dose. From the plasma drug level-time profiles after the last dose, it was obvious that the high plasma itraconazole levels did not obey first-order kinetics and that the elimination of itraconazole was saturable. Therefore, the plasma drug concentrations in the postdistribution phase were analyzed by use of the Michaelis-Menten approach. On the basis of V_{max} and K_m, the apparent first-order half-life describing elimination when plasma drug concentrations were below the K_m was 24 h. This value is in good agreement with the half-life of 1 day observed after a single dose.

Steady-state concentrations of the metabolite hydroxyitraconazole were also attained after 2 weeks of treatment. For hydroxyitraconazole, the AUC for a dosing interval at steady state was increased fivefold in comparison with the AUC_{0-∞} after a single dose. From Fig. 4, it is obvious that the elimination of hydroxyitraconazole also occurred via a saturable process.

The results of this study show that the currently marketed capsules containing itraconazole-coated sugar spheres should be taken with food to ensure optimal absorption. On repeated dosing (200 mg twice daily), steady-state concentrations in plasma of itraconazole and the active metabolite hydroxyitraconazole were attained after 2 weeks of treatment. The elimination of itraconazole and hydroxyitraconazole occurs via saturable processes.

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