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Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole

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Abstract. The influence of food on the pharmacokinetics of the triazole antimycotics fluconazole and itraconazole was investigated in a randomised, parallel group, single dose study in 24 healthy subjects. Each group took either a 100 mg capsule of fluconazole or a 100 mg capsule of itraconazole, pre-prandially or after a light meal or a full meal, in a three-way crossover design. Gastric and intestinal pH were measured with a co-administered radiotelemetric pH capsule, and gastric emptying time of the capsule (GET) was taken as the maximum gastric residence time of drug and food.

The plasma AUC and C_{max} of itraconazole were significantly different under the various conditions and the mean AUC was greatest after the full meal. The bioavailability (90% confidence intervals) of itraconazole relative to that after the full meal, was 54% (41–77%) on an empty stomach and 86% (65–102%) after a light meal. The criteria for bioequivalence were not attained. In contrast, the bioavailability (90% CI) of fluconazole relative to the full meal was 110% pre-prandially (100–115%) and 102% after the light meal (88–103%), and the criteria for bioequivalence were attained.

Itraconazole absorption was promoted by low stomach pH, long gastric retention time and a high fat content of the coadministered meal, whereas the pharmacokinetics of fluconazole was relatively insensitive to physiological changes in the gastrointestinal tract.

Key words: Fluconazole, Itraconazole; pharmacokinetics, food interaction, gastric emptying time, pH radiocapsule

The rate and extent of the gastrointestinal absorption of a drug are determined by the physicochemical properties of the compound and its pharmaceutical formulation, and they may also vary with physiological conditions, such as pH and gastric emptying [1, 2]. The presence of food in the stomach can exert an influence on the release, dissolution and gastroduodenal transport of a drug. While belonging to the same chemical class of triazoles, the antifungals fluconazole and itraconazole are very different in molecular weight, lipophilicity, and solubility in water. Itraconazole has high lipophilicity (P = 460000) and is almost insoluble in water and in dilute acids (less than $5\,\mu g \cdot ml^{-1}$ [3]), whereas fluconazole is hydrophilic (solubility in water $6\,mg \cdot ml^{-1}$) and slightly lipophilic ($P = 1.6$ [4]). Itraconazole is a weak base (pk_a 3.7) and is only ionised at a low pH, as in gastric juice. Both drugs have been shown to be well absorbed orally. For itraconazole, however, evidence has been found that drug administration on an empty stomach reduces its systemic bioavailability [3], and very low plasma concentrations, associated with reduced efficacy and treatment failure, were observed in patients with dermatomycoses, superficial candidiasis and pityriasis versicolor [5], when the drug was taken in the fasting state. In contrast, the absorption of fluconazole did not appear to be affected by food to a significant extent [4].

In the light of large individual and cultural variations in nutritional habits, and keeping in mind clinical states with dietary restrictions or gastrointestinal disease, more detailed information on the effect of food on triazole absorption is essential for therapy with these drugs.

The aim of the present study was to investigate the interaction of food with the oral absorption of fluconazole and itraconazole. Gastric pH was determined in parallel by an ingestible pH radiocapsule, and the passage of this capsule into the duodenum was recorded as a measure of the gastric emptying time of each drug [6].

Subjects and methods

Subjects

Informed written consent was obtained from 24 healthy male and female volunteers. Subjects with clinically significant abnormalities, or with a history of any significant medical disorder were excluded from the trial. Volunteers were randomly assigned to the fluconazole or itraconazole groups; the two groups were matched with respect to

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Table 1. Pharmacokinetic parameters (means (SD) [CV]) and relative bioavailabilities (BA) of fluconazole and itraconazole after preprandial (12 h fasting) and post-prandial (light meal and full meal) oral administration of a 100 mg capsule of each drug to 12 healthy volunteers. BAs were calculated on the basis of AUC; the reference was the individual AUC after the full meal administration

	Fluconazole			Itraconazole		
	Pre-prandial	Light meal	Full meal	Pre-prandial	Light meal	Full meal
AUC [hμgml^{-1}]	113 (17.9) [16%]	101 (15.7) [16%]	106 (23.6) [22%]	1.62 (1.13) [70%]	2.29 (1.18) [52%]	2.75 (1.43) [52%]
C_{max} [μgml^{-1}]	2.34 (0.51) [22%]	2.27 (0.52) [23%]	2.22 (0.48) [22%]	0.11 (0.06) [55%]	0.21 (0.12) [57%]	0.23 (0.11) [48%]
t_{max} [h]	3.08 (0.79) [26%]	3.08 (0.67) [22%]	3.50 (1.00) [29%]	3.33 (1.15) [35%]	3.67 (0.78) [21%]	4.17 (1.03) [25%]
$t_{0.5}$ [h]	36.80 (7.43) [20%]	33.4 (4.10) [12%]	35.0 (6.58) [19%]	20.7 (16.6) [80%]	16.99 (7.19) [42%]	17.5 (9.70) [55%]
BA 90% confidence interval	100–115	88–103	–	41–77	65–102	–
Median	1.10	1.02	–	0.54	0.86	–
Range	(0.87–1.51)	(0.69–1.20)	–	(0.23–1.10)	(0.40–1.43)	–

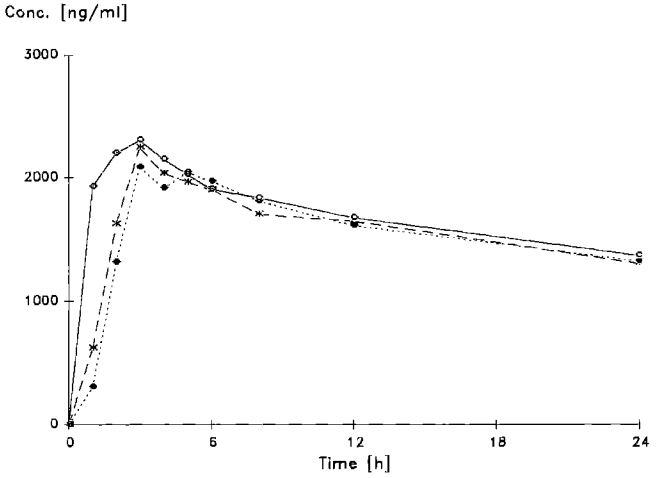

Fig. 1. Mean concentration time-curves (0–24 h) after pre-prandial [12 h fasting (○)] and post-prandial [light meal (*) and full meal (●)] oral administration of 100 mg fluconazole to 12 healthy volunteers

sex, age, height, weight and smoking habit. Volunteers in the fluconazole group had a mean age of 37 y (range 18–49 y), a mean weight of 72 kg (49–93 kg), and a mean height of 170 cm (160–184 cm).

The corresponding data for the itraconazole group were 34 y (22–51 y), 70 kg (52–90 kg), and 171 cm (160–189 cm). There were 7 M (1 smoker) and 5 F volunteers (2 smokers) in each group.

The study was approved by the Ethical Committee of the Bayerische Landesärztekammer (Bavarian Provincial Chamber of Medicine).

Study design

Fluconazole capsules (Diflucan®, Pfizer, France) 100 mg were compared with itraconazole capsules (Sempera®, Janssen, Germany) 100 mg in a parallel, matched group study. Food intake was randomised according to a 3-way cross-over design.

Each volunteer was examined after three different eating patterns: (A) 12 hours of fasting, (B) light meal: two slices of white toaste, 1 spoonful of jam, and 2 cups (300 ml) decaffeinated coffee (estimated calorific value 1000 kJ), and (C) full meal: two toasted slices of white bread, 40 g butter, 2 fried eggs, 2 sausages (about 100 g), 1 rasher of bacon (about 25 g), and 2 cups of decaffeinated coffee (estimated calorific value 3600 kJ). The drug was administered within 5 min after completion of the breakfast, with 100 ml tap water. The pH capsule was swallowed immediately before taking the drug.

No further food or drink was allowed up to 5 h after drug administration (fasting group 3 h). Alcohol, caffeine and nicotine were forbidden. Blood samples were obtained immediately before drug administration and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 h thereafter. A washout phase of 2 weeks was observed.

pH Measurements and drug analysis

Gastrointestinal pH was measured using a freely moving pH sensitive radiotelemetry capsule (Flexilog 1010 ambulatory pH system, Oakfield Instruments Ltd., Eynsham, UK). The 24 × 7 mm capsule consists of a glass electrode with integral reference cap and battery. The signal frequency of the microtransmitter, which depends on intraluminal pH, is received by an external belt antenna, enabling continuous measurement and automatic recording of pH as the capsule passes through the GI tract. Measurements were limited to 12 h after drug intake.

Individual pH statistics were provided by the Flexilog software. Gastric emptying of the capsule (GET) was measured by the typical and stable pH increase of at least 3 units when the capsule reached the duodenum. For the determination of gastric and intestinal pH, the total time considered was the period up to GET and the first 5 h after gastric emptying, respectively (assuming a mean small bowel transit time of 5 h [2, 7]).

The plasma concentrations of fluconazole were measured using a gas chromatographic method with electron capture detection. Preparation of the samples was performed by a robotic method (Zymark II laboratory robot, Zymark, USA), based on a published procedure [4].

The plasma concentrations of itraconazole were assayed by HPLC, combining the sample processing used by Woestenborghs et al. [8] with fluorescence detection at 260 nm excitation and 365 nm emission, as used by Allenmark et al. [9].

Evaluation

C_{max} and t_{max} were taken from the individual curves of plasma concentration against time. $t_{0.5}$ was calculated using least squares regression analysis of the terminal phase. The AUCs were estimated by the linear trapezoidal method. Relative bioavailability was calculated as

Table 2. Gastric emptying time (GET) and gastrointestinal pH measured by an ingestible radiotelemetry capsule after pre-prandial (12 h fasting) and post-prandial (light meal and full meal) administration

	Pre-prandial (A)				Light meal (B)				Full meal (C)				Significance of differences
	n	Median	Q_{75}–Q_{25}	Range	*n*	Median	Q_{75}–Q_{25}	Range	*n*	Median	Q_{75}–Q_{25}	Range	
Gastric pH	23	2.00	0.90	1.0–4.0	23	1.50	1.20	1.0–3.1	22	1.55	1.40	1.0–2.8	$P < 0.05$ A/B
pH of small bowel	20	7.50	1.05	5.5–8.5	23	7.40	0.50	5.5–8.5	8	7.25	1.25	6.0–8.0	NS –
GET (min)	23	35	80	2–720	23	105	75	45–245	22	720	310	255–720	$P < 0.05$ A/B, C/B, A/C

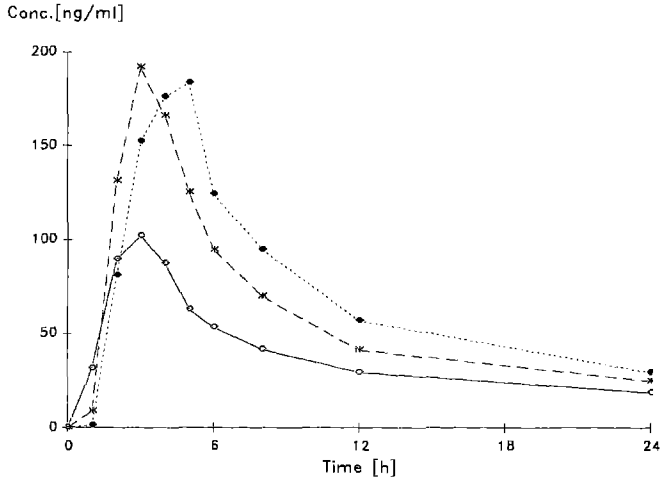

Fig. 2. Mean concentration time-curves (0–24 h) after pre-prandial [12 h fasting (○)] and post-prandial [light meal (*) and full meal (●)] oral administration of 100 mg itraconazole to 12 healthy volunteers

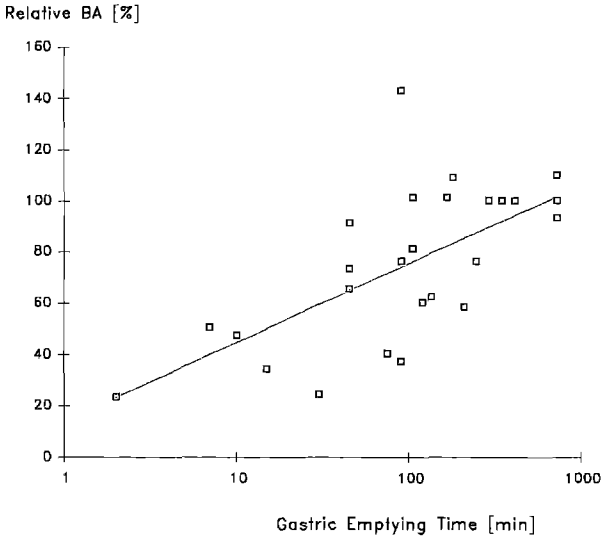

Fig. 3. Correlation of individual relative bioavailabilities (BA) of itraconazole and gastric emptying times (GET), plotted on a logarithmic scale. Itraconazole 100 mg capsule was given pre-prandially (after 12 h of fasting), after a light meal, and after a full meal, to 12 healthy volunteers. Relative BAs were calculated by reference to the AUC after administration of the full meal. The correlation coefficient is 0.66 ($P < 0.0001$)

the ratio of the appropriate AUC to the AUC after the full meal as the reference treatment.

Ninety percent confidence intervals were calculated for the differences in AUCs measured under the various conditions of administration. Analysis of variance (ANOVA) followed by the Scheffé test was carried out on all parameters. For GET and pH the data were previously ranked [10]. Differences between the itraconazole and the fluconazole groups were tested by Wilcoxon's rank sum test. Pearson correlation coefficients were determined for the individual relative bioavailabilities and the log GET of both groups. An error probability of $P < 0.05$ was regarded as statistically significant.

Results

All volunteers completed the study as scheduled and the study drugs were well tolerated.

Mean concentration-time curves were depicted in Fig. 1 (fluconazole) and Fig. 2 (itraconazole). The pharmacokinetic parameters are compared in Table 1. For itraconazole, AUC and C_{max} were significantly influenced by food; Scheffé tests showed significant differences between each condition (light meal, full meal, fasting). The 90% confidence intervals for the pre-prandial bioavailability (BA) and the BA after the light meal lay between 41 and 77%, and between 65 and 102%, respectively (relative to the full meal).

For fluconazole, the AUC was significantly influenced by food, with a significant Scheffé test for the comparison of pre-prandial and light meal application. However, 90% confidence intervals for the relative bioavailabilities after pre-prandial and light meal administration were within the classical limits of bioequivalence (100–115%, and 88–103%, respectively, relative to administration of the heavy meal). C_{max} of fluconazole was not significantly influenced by food.

For both drugs, t_{max} had a tendency to be higher after the full meal, but without reaching statistical significance. Half-lives of fluconazole (about 35 h) and itraconazole (about 18 h) were not changed by food. The coefficients of variation of the AUC, C_{max} and $t_{1/2}$ were of the order of 19% for fluconazole, and 57% for itraconazole, respectively.

The gastrointestinal pH and gastric emptying times in the three groups after the different eating conditions are shown in Table 2. Gastric pH was slightly influenced by food, with a significant difference between light meal and pre-prandial conditions. The pH of the small bowel was not significantly altered by food. Gastric emptying times were significantly different between each of the groups. There were no statistically significant differences in gastric pH and GET between the fluconazole and the itraconazole groups under the three conditions.

The relationship between the relative bioavailability of itraconazole and the gastric emptying time is shown in Fig. 3; the correlation coefficient was $r = 0.66$ ($P < 0.0001$). For fluconazole, the corresponding correlation coefficient was $r = -0.18$ (NS).

In the itraconazole (fluconazole) group, the physiological data after 3 (1) administrations could not be evaluated due to missing values related to technical failure of the pH capsule.

Discussion

The results of the pharmacokinetic analyses are in good conformity with data previously presented for fluconazole [11] and itraconazole [5]. High interindividual variability of the itraconazole AUC has been described elsewhere [12]; in our data, variability, in terms of the coefficient of variation of the AUC, C_{max} and $t_{0.5}$, was about three-times higher for itraconazole than for fluconazole. For example, there was approximately a 20-fold difference between volunteers in the pre-prandial maximum concentration (C_{max}) of itraconazole, which ranged from 10.3 $ng \cdot ml^{-1}$ to 223 $ng \cdot ml^{-1}$. For fluconazole, the pre-prandial C_{max} ranged from 1590 to 3180 $ng \cdot ml^{-1}$. There was no therapeutically relevant effect of food intake on the pharmacokinetic properties of fluconazole, and the criteria of bioequivalence were fullfilled.

Comparison of pH and GET between the parallel groups of subjects showed that the influence of food on these physiological parameters did not differ significantly between the two groups. Thus, the observed differences in the pharmacokinetic behaviour between the two drugs are most probably not related to physiological differences between the groups of volunteers.

Insoluble components in the stomach with a diameter in the range of the pH capsule are normally passed into the intestine after all digestible components have been released [13]. In previous studies, the gastric residence time of the telemetric device was found to be correlated with but to be consistently longer than the emptying half-time estimated by simultaneous isotopic measurements in the same subjects fed a liquid meal [14]. The gastric emptying time (GET) measured in this study can be interpreted, therefore, as the maximum residence time of food and drug in the stomach.

The short residence time of pre-prandial itraconazole (median 45 min) in the stomach is consistent with its early appearance in plasma (see Fig. 2). However, the relative bioavailability in this group was low, and a considerable amount of drug appeared to escape absorption. Absorption of the lipophilic base itraconazole was promoted by low stomach pH, a high gastric retention time, and a high fat content of the coadministered meal.

In the fluconazole group there was no indication of a correlation between physiological parameters and drug absorption.

The present results are in accordance with previous results, which demonstrated that changes in gastric pH did not influence the pharmacokinetics of fluconazole [15].

A dissolution profile that is not sensitive to physiological changes in pH is a property that will favour reliable absorption of a drug. The robustness of the pharmacokinetics of fluconazole could be an advantage in all clinical conditions associated with gastric hypochlorhydria, especially in AIDS gastropathy [16, 17]. Furthermore, many patients requiring antifungal therapy, eg. those with AIDS or those receiving cancer chemotherapy, may have extreme difficulty in eating normally, and it would not be possible for them to take antifungal medication with a full meal to promote maximum absorption.

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