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Influence of Food on the Pharmacokinetics of Ketoconazole

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Eight healthy adults were given single oral doses of ketoconazole (200, 400, 600, and 800 mg) in the fasting state and with a standard breakfast at weekly intervals according to a balanced block design. Concentrations in serum were measured up to 32 h after the dose. Food did not reduce ketoconazole absorption or significantly alter peak ketoconazole concentrations in serum, though there was a food-related delay in achieving peak concentrations. At the 400- and 600-mg doses, food appeared to enhance absorption, but this effect was not seen at the 800-mg dose. With an increase in dose, the half-life and area under the serum concentration-time curve increased disproportionately, suggesting that the pharmacokinetics of ketoconazole may be dose dependent. Up to the 800-mg dose, the elimination of ketoconazole did not appear to be saturable. Administration of the drug with food is unlikely to be a cause of therapeutic failure.

Ketoconazole is a new imidazole derivative which is active against both superficial and deep fungal infections after oral administration (11, 12). The single-dose pharmacokinetics of ketoconazole in normal subjects have previously been reported (6, 8, 14) and have also been investigated in patients with different fungal infections (2, 3, 7, 8) and in immunocompromised patients (9, 13).

It is recommended by the manufacturers that the drug be given with food to improve absorption. This recommendation is based on the higher ketoconazole concentrations found 1 and 2 h postdose in the sera of 30 patients with onychomycosis when the drug was given with food (7). More recently, a reduction in ketoconazole absorption was found when single doses were taken with meals (2), but this was not significant compared with the fasting state. However, another study (14) found that breakfast significantly reduced the absorption of ketoconazole, and another study (6) suggested a possible improvement in ketoconazole absorption when given with food.

In animal studies, ketoconazole kinetics appear to be dose dependent (1). A feature of ketoconazole kinetics noted in single-dose studies in humans is the relationship between ketoconazole dose and elimination: the half-life of ketoconazole increases as the dose is increased. In addition, the area under the serum concentration-time curve increases disproportionately with the increase in dose (6, 8). We therefore examined the kinetics of ketoconazole over a wide dose range to determine whether food altered absorption even at high doses and to determine whether the previously observed relationship between dose and elimination was present at doses above 400 mg.

MATERIALS AND METHODS

Three male and five female healthy adults aged 20 to 31 years (mean, 23 years) and weighing between 50 and 75 kg (mean, 64 kg) gave informed consent to inclusion in this study, which was approved by the medical ethics committee. A full blood count, plasma and urea electrolyte concentrations, and standard liver function tests were performed before treatment and 1 day after each dose of ketoconazole. No subject had any clinical or biochemical evidence of hepatic or renal impairment. Each subject received eight doses of ketoconazole (Nizoral; Janssen Pharmaceutical Ltd.) at weekly intervals. The doses were 200, 400, 600, and 800 mg taken with 100 ml of water after an overnight fast, and the same doses were taken at the end of a standard breakfast. The order of treatments was randomized according to a balanced block design. The standard breakfast consisted of 24.5 g of fat, 81.3 g of carbohydrate and 18.2 g of protein (energy value, 603 kilocalories or 2,524 kJ) taken with 150 ml of coffee. Venous blood samples were collected just before the first dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 28, and 32 h after each dose. Serum was separated and frozen for later analysis of ketoconazole by a microbiological agar well diffusion method (5). The lower limit of sensitivity of this assay was 0.12 mg/liter. The interassay coefficient of variation was less than 5% for determinations in the range of ketoconazole concentration in serum in this study.

The half-life of ketoconazole in serum was calculated from least-squares regression analysis of the log serum concentration-time profile. The area under the serum concentration-time curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity. Statistical comparisons were made by using Student's t test for paired data. Significance was assumed at $P < 0.05$ (two-tailed test).

RESULTS

The mean concentration in serum versus time plots at each dose in the fasting state and with food are shown in Fig. 1. AUC, half-life ($t_{1/2}$), peak concentration in serum (C_{max}), and time to reach peak concentration in serum (T_{max}) for each dose with and without food are shown in Table 1. The increases in AUC and C_{max} were disproportionately greater than the increase in dose. In addition, a progressive increase in $t_{1/2}$) with an increase in dose was observed. The T_{max} also increased as the dose increased. In the fasting state, the AUC of ketoconazole at doses of 400, 600, and 800 mg increased by factors of 2.8, 5.8, and 11.5, respectively, compared with the 200-mg dose. The corresponding values for the same doses given with food were 4.3, 7.9, and 11.1, respectively (Table 1).

Food did not reduce the absorption of ketoconazole at any of the doses. The improvement of ketoconazole absorption by food was variable. At the 200-mg dose, administration

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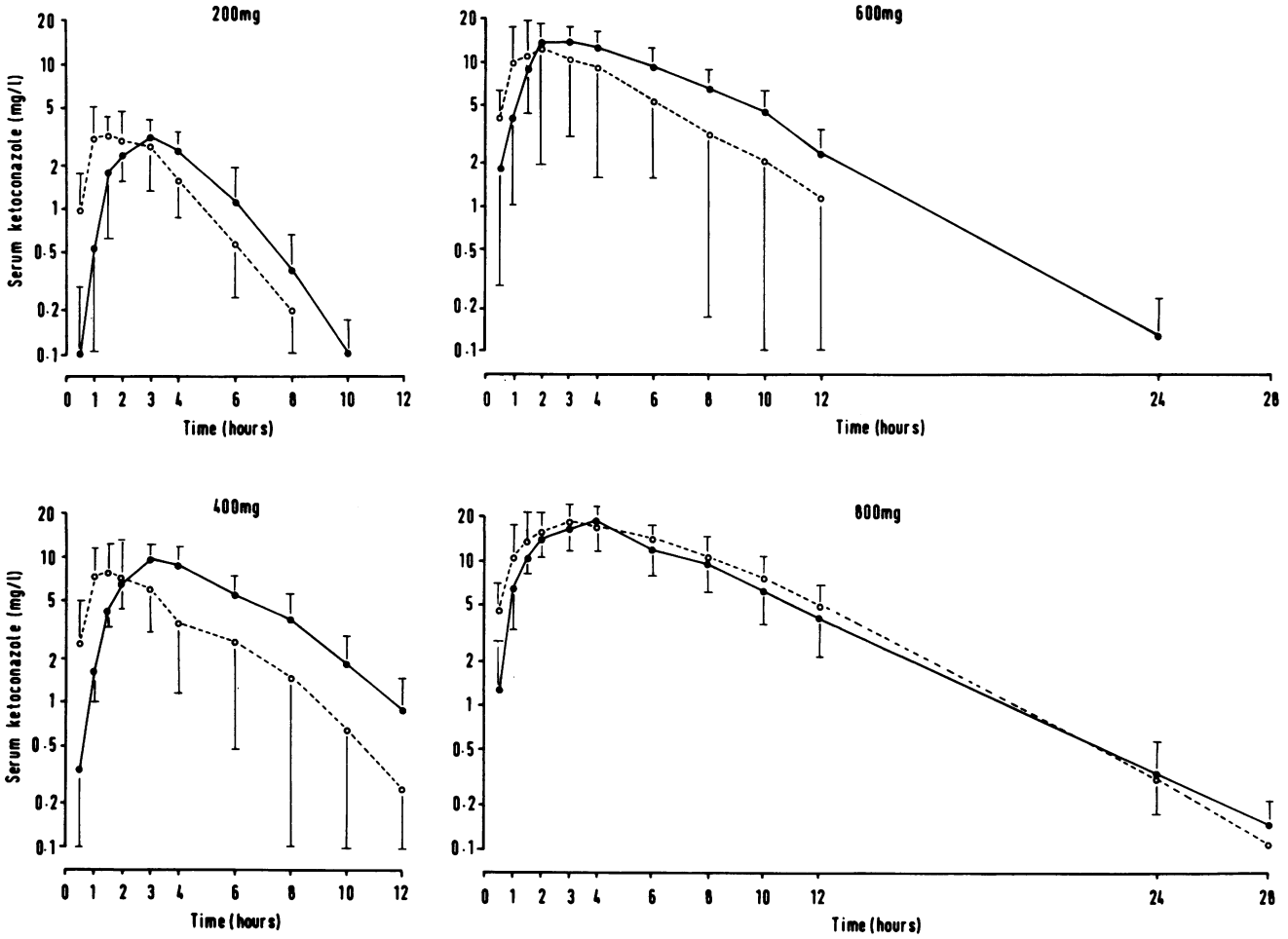

FIG. 1. Mean ketoconazole concentrations in serum in eight subjects given 200-, 400-, 600-, and 800-mg doses in the fasting state (○) and with breakfast (●). Vertical bars represent standard deviations.

with food resulted in no significant increase in AUC or $t_{1/2}$, whereas reduction in C_{max} and increase in T_{max} tended towards statistical significance ($2P = 0.08$ and 0.06, respectively). Administration with food resulted in an almost significant increase in the AUC ($2P = 0.056$) and the $t_{1/2}$ ($2P = 0.08$) at the 400-mg dose. At this dose the C_{max} was unchanged, but there was a significant food-related increase in T_{max}. The 600-mg dose, when given with food, resulted in a nonsignificant 45% increase in AUC, significant increases in $t_{1/2}$ and T_{max} but no change in C_{max}. The kinetics of ketoconazole were virtually unaltered by food at the 800-mg dose. (Table 1 and Fig. 1).

Four subjects complained of mild dizziness and nausea, sometimes with headache, occurring between 1 and 3 h after the 600- and 800-mg doses. These side effects were not affected by coadministration with food. No abnormalities were detected in the hematological or the biochemical index after any of the doses of ketoconazole.

DISCUSSION

Our study clearly shows that food does not impair ketoconazole absorption at doses up to 800 mg. Though food tended to improve absorption at the 400- and 600-mg doses, these changes were not significant. Our findings are in

TABLE 1. Effect of food on single doses of ketoconazole in eight subjects[a]

Ketoconazole dose (mg)	AUC (mg · h/liter)		$t_{1/2}$ (h)		C_{max} (mg/liter)		T_{max} (h)	
	Fasting	Food	Fasting	Food	Fasting	Food	Fasting	Food
200	12.9 ± 1.5	13.6 ± 1.2	1.37 ± 0.03	1.43 ± 0.08	4.36 ± 0.54	3.29 ± 0.22	1.57 ± 0.25	2.62 ± 0.32
400	37.2 ± 8.6	59.2 ± 6.2	1.90 ± 0.15	2.45 ± 0.27	9.06 ± 1.65	10.64 ± 0.73	1.62 ± 0.15	3.00 ± 0.27[b]
600	74.5 ± 20.3	107.9 ± 10.3	2.38 ± 0.63	3.15 ± 0.13[b]	15.10 ± 3.96	15.40 ± 1.55	1.87 ± 0.28	2.82 ± 0.32[c]
800	148.8 ± 28.7	151.2 ± 16.6	3.75 ± 0.38	3.62 ± 0.20	20.97 ± 2.43	19.22 ± 1.99	2.78 ± 0.30	2.85 ± 0.38

[a] All values represent mean ± standard error.
[b] $2P = 0.01$ compared with the fasting value.
[c] $2P = 0.05$.

agreement with those of Gascoigne et al. (8) but contradict the results of two other studies (2, 14). These previous investigations were limited, however, to the examination of the effect of food on 200-mg doses of ketoconazole. We are unable to explain the discrepancy between the findings of the present study and the results of the two other studies (2, 14). It has been suggested that ketoconazole absorption may depend upon the solubilizing effect of bile and that food, in particular the fat content, may enhance absorption by stimulating bile secretion. The standard breakfast used in the present study was very similar to that used by others (14), and particular emphasis was placed on achieving a similar fat content.

It has recently been recognized that food-associated changes in hepatic blood flow may decrease the first-pass metabolism of high-clearance drugs and result in higher AUCs after oral dosing with food (15). Indeed, food may also alter the pharmacokinetics of an intravenously administered high-clearance drug (4). Data from animal studies suggest that ketoconazole may undergo first-pass metabolism (10). Consequently, the food-related increase in ketoconazole may be due to transient changes in hepatic blood flow.

The data from this study also show that the pharmacokinetics of ketoconazole are dose dependent. These observations in humans extend those made previously over the dose range of 100 to 400 mg (8) and confirm the original observations in mice (1). In the present study, the elimination phase was monoexponential at all doses. Above a concentration in serum of 0.12 mg/liter, we did not observe the slower elimination phase noted by Gascoigne et al. (8). The most conclusive evidence of dose-dependent pharmacokinetics is provided by the increase in half-life with the increase in dose in this study.

The $t_{1/2}$ of ketoconazole has shown some variation in single-dose and multiple-dose studies (2, 3, 5, 6, 8, 13, 14). Some of the more extreme values (9) are difficult to explain, even after allowing for the different methods used. Most studies have shown that $t_{1/2}$ increases with chronic dosing (3, 5, 13). However, in one study the $t_{1/2}$ of ketoconazole in patients with leukemia was found to be less than 1 h (9). This discrepant result may be due to pooling of data from different patients and inadequate sampling after 6 h (9).

In practical therapeutic terms, it should be noted that in the present study food had almost no effect on C_{max} at any of the doses used. Also, the food-associated delay in T_{max}, though statistically significant at the 400- and 600-mg doses, is not of clinical significance. In addition, the prolongation of $t_{1/2}$ noted with food is of small magnitude and, in the clinical setting, would not influence the dosing interval. On the basis of our findings, ketoconazole may be given with or without food. However, it should be noted that the effects of food on the multiple-dose kinetics of ketoconazole at steady state have not yet been determined. Administration of the drug with meals is unlikely to be the cause of lower drug concentrations in serum or be a contributory factor in patients who experience apparent therapeutic failure with ketoconazole.

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