Pharmacokinetics of vibunazole (BAY n 7133) administered orally to healthy subjects

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The role of gastric acidity in the absorption of the new antifungal drug vibunazole was studied in six healthy volunteers. Vibunazole was administered orally as 400 mg tablets to fasting subjects under three conditions: after 400 mg cimetidine orally, after 30 ml diluted hydrochloric acid orally, and alone. Plasma concentrations of vibunazole were determined with HPLC. The plasma concentration profile of vibunazole could be described adequately by a one-compartmental open model with first-order absorption. Kinetic parameters after oral administration did not differ between the three modes of administration. The mean peak time was 1 h 29 min (after lag-time). The mean peak concentration was 2·76 mg/l. The mean elimination half-life of vibunazole was 2 h 22 min. The mean absorption lag-time was 30 min, with considerable variation.

Introduction

Recently, a new class of oral anti-mycotic drugs has been developed. Vibunazole is a triazole compound with a mode of action similar to that of ketoconazole, an imidazole-derivative. Its antimycotic spectrum differs from that of ketoconazole in that the *Aspergillus* species are sensitive to vibunazole (Meunier-Carpentier *et al.*, 1983). Like ketoconazole, vibunazole is absorbed after oral administration (van der Meer *et al.*, 1980). Because the absorption of ketoconazole is greatly impaired at low gastric acidity (van der Meer *et al.*, 1980) the present study was undertaken to establish the influence of gastric acidity on the absorption of vibunazole in healthy volunteers.

Materials and methods

Experimental design

Subjects were six healthy volunteers (5 female, 1 male), all of whom had normal renal and hepatic function and used no other medication. The volunteers, who were informed in detail about the purpose and design of the experiment, were divided into two groups of three subjects each. Each subject received a tablet containing 400 mg vibunazole to be taken orally on three occasions at intervals of at least two weeks and under three different conditions according to a Latin square: fasting without any additional medication; fasting two hours after oral administration of 400 mg cimetidine; fasting 1 h after oral administration of 30 ml 0·1 N hydrochloric acid.

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Determination of plasma concentrations

Plasma concentrations of vibunazole were measured by reversed-phase HPLC, as a modification of the methods earlier described (Alton, 1980; Andrews *et al.*, 1981). The HPLC system consisted of the following components: a solvent-delivery pump LC 414 (Kipp & Zonen, Delft, The Netherlands), a model U6K injector (Waters Ass. Milford, Mass., USA), a variable wavelength UV-detector (KRATOS-773, Kipp & Zonen, Delft, The Netherlands) and a flat-bed recorder BD-40 (Kipp & Zonen, Delft, The Netherlands). The column (length 10 cm, ID 3·0 mm) was packed with MOS-hypersil (particle-size 5 μm).

The following conditions were employed: UV-detector setting at 231 nm, a flow-rate of 1·5 ml/min, and a chart speed of 2 mm/min. Stationary phase: MOS-hypersil 5 μm. Mobile phase: 0·05 M (NaH_2PO_4/NaOH) buffer (pH 7·5)—acetonitrile (64:36 v/v). The retention time of vibunazole in this system is 5·5 min.

Stock solutions were prepared by dissolving 10 mg of vibunazole in 50 ml of methanol. Appropriate amounts of this standard solution were added to blank plasma to yield concentrations of 0·2, 0·5, 1·0, 2·0, 5·0 and 10·0 mg/l of vibunazole.

An aliquot (250 μl) of plasma was transferred to a 10 ml test tube, alkanilized with 50 μl M NaOH solution and then extracted with 3 ml of n-hexane by vortex mixing for 10 sec. Separation of the layers was facilitated by centrifuging for 1 min at 1000 g. Two ml of the organic phase was transferred to a 20 ml glass vial. The plasma was re-extracted by adding 2 ml of n-hexane to the test tube and repeating the procedure. The collected organic phases were evaporated in a gentle nitrogen stream. The residue was dissolved in 250 μl of a mixture of acetonitrile and water (1/1). All concentrations of vibunazole in the unknown plasma samples were determined on the day of the experiment.

The concentrations of vibunazole were calculated from the peak heights in the unknown plasma samples and the spiked samples as prepared for the calibration curves. It appeared that the use of an internal standard was not necessary because of the great reproducibility of the assay procedure as described above. The relationship between the peak heights of the aqueous standards and the concentrations of vibunazole as well as that between standards and the spiked plasma extracts appeared to be linear, with correlation coefficients amounting to 0·999 and 0·998 respectively, in the concentration range from 0·2 to 10·0 mg/l. The recovery was calculated as 83% (s.d. 0·8%).

Pharmacokinetic analysis

Apparent elimination rate constants were calculated from the terminal slope (from 3 h onwards) of the log plasma concentration time curve. The area under the plasma concentration time curve (AUC) was established according to the trapezoid method, extrapolated to infinity.

Absorption was calculated according to Wagner & Nelson (1963) as

$$\frac{A_t}{V} = C_t + k_e{}^*\text{AUC}_t, \tag{1}$$

in which A_t is the amount absorbed at time t, V is the apparent volume of distribution, C_t the concentration at time t, k_e the elimination rate constant, and AUC_t the area under the plasma concentration time curve from 0 to time t.
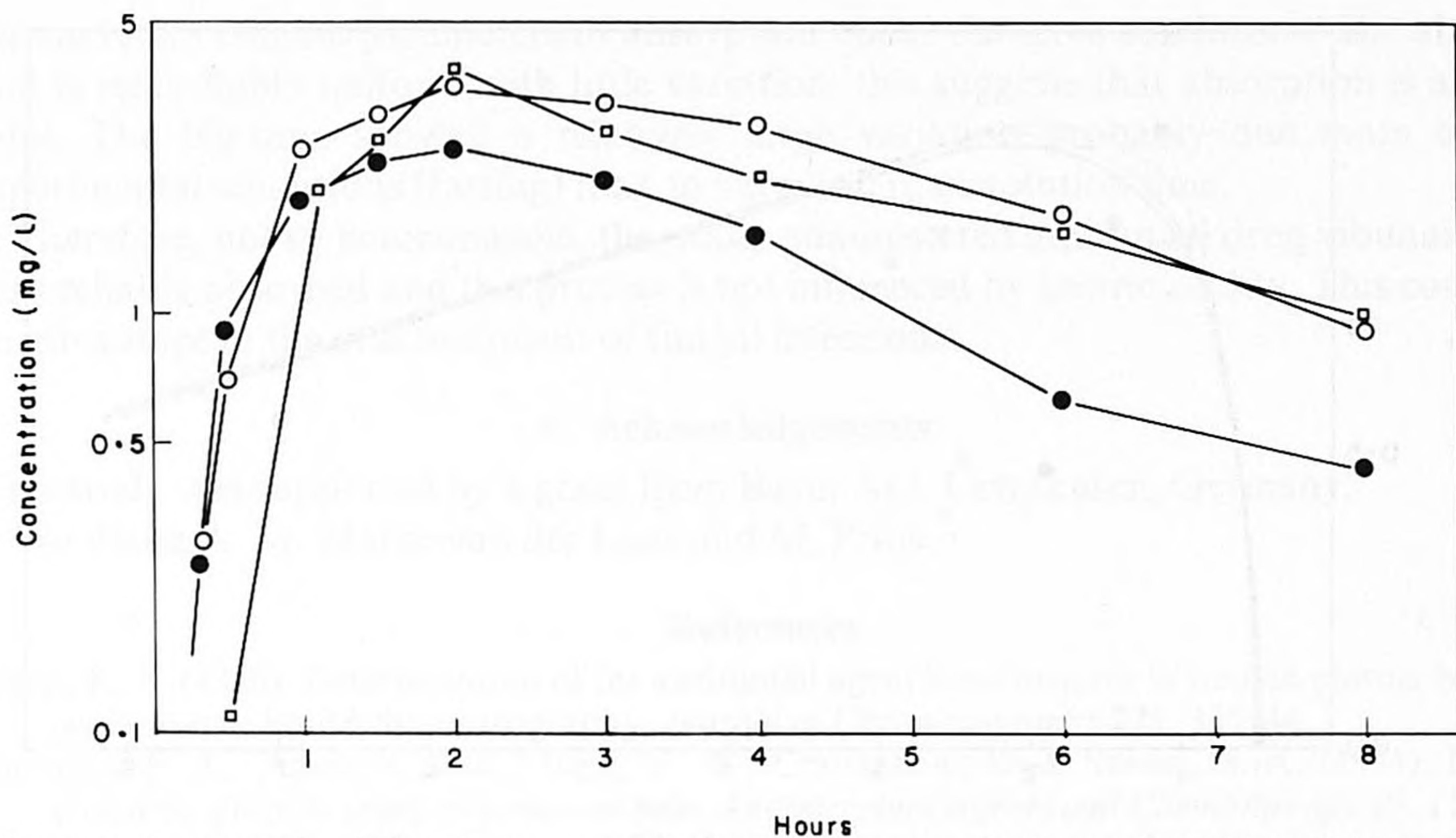
Figure 1. An example of the plasma concentration time curves of vibunazole. Tablets of 400 mg were administered without an adjuvant (○) or together with 30 ml 0·1 N hydrochloric acid (□) or 400 mg cimetidine (●).

Table I. Pharmacokinetic parameters of vibunazole after oral administration (mean + S.D.)

	Conditions of administration		
	alone	with cimetidine	with hydrochloric acid
K_e (h^{-1})	0·277 (0·07)	0·312 (0·1)	0·29 (0·07)
K_a (h^{-1})	1·25 (0·27)	0·15 (0·59)	0·51 (0·6)
AUC$_{0-\infty}$ (mg/l.h.)	14·2 (3·6)	14·2 (2·1)	15·2 (3·3)
Lag-time (min.)	26·1 (14·7)	30·1 (12·3)	32·0 (13·3)

The calculated values of A_t/V were subtracted from the apparent maximal value of A_t/V and plotted logarithmically against time. The absorption rate constant k_a and the absorption lag-time T were calculated according to the following equation;

$$\frac{A_t}{V} = \frac{A_{max}}{V}(1 - e^{-k_a(t-T)}).$$

(2)

The time of maximal concentration was calculated as

$$t_{max} = \frac{\ln k_a - \ln k_e}{k_a - k_e},$$

(3)

and the maximal concentration as

$$C_{max} = AUC \times \frac{k_a \times k_e}{k_a - k_e} e^{-k_e(t_{max} - T)} - e^{-k_a(t_{max} - T)}.$$

(4)

Results

A representative example of concentration-time curves after oral administration of 400 mg vibunazole is given in Figure 1. Calculated pharmacokinetic parameters for all volunteers are given in Table I. Using the mean values of the pharmacokinetic
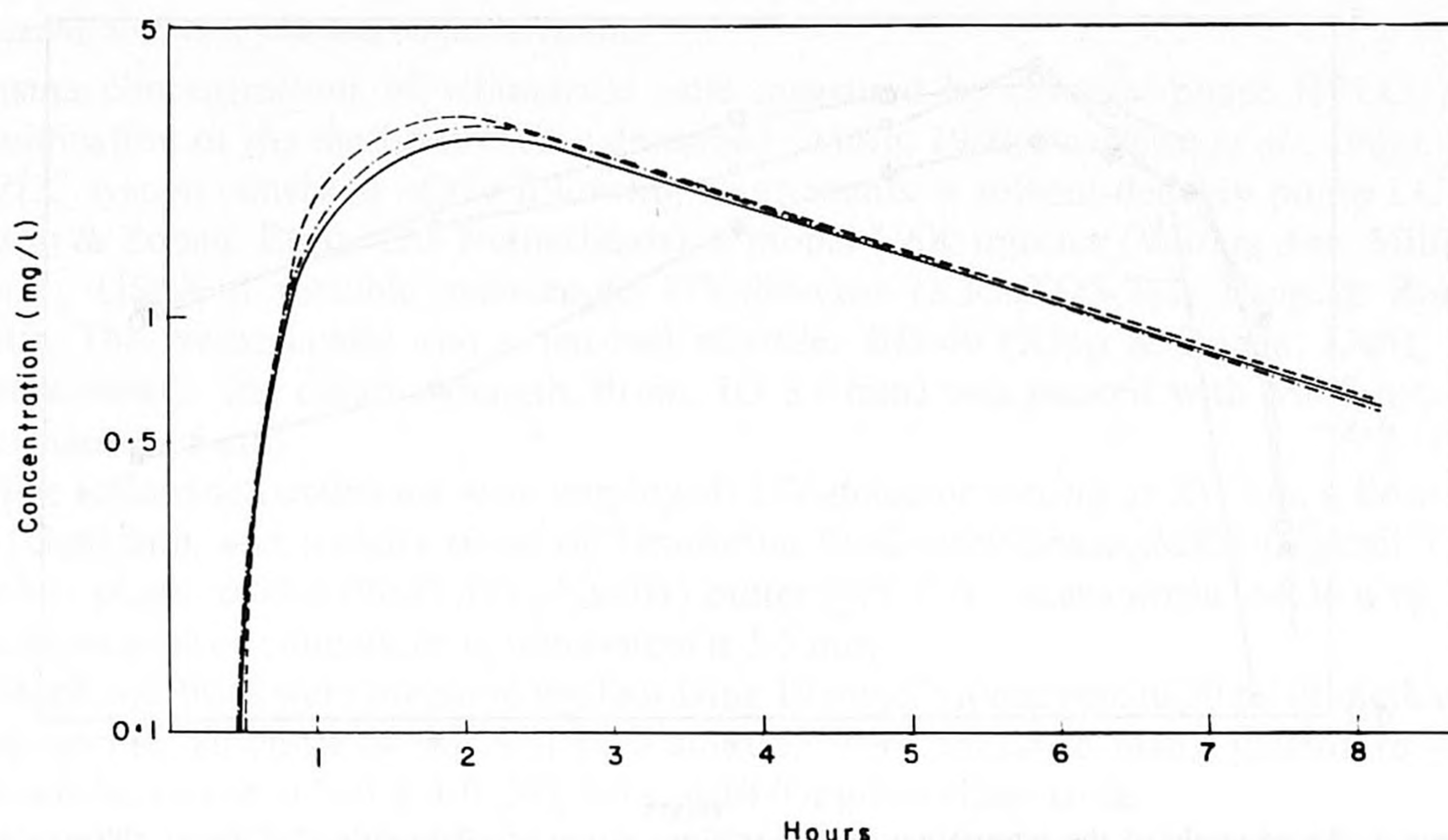
Figure 2. Plasma concentrations of vibunazole after 400 mg orally. The curves were constructed with the mean values of the pharmacokinetic parameters in six volunteers. Without an adjuvent ——, with 30 ml 0·1 *N* hydrochloric acid – – – –, and 400 mg cimeditine –·–·–·–.

parameters for the three conditions, average plasma concentrations curves were constructed (Figure 2).

Analysis of variance showed that the apparent elimination rate constants did not differ significantly between the different modes of administration ($F_{2, 10} = 0·30$; $P > 0·05$). The mean elimination rate constant corresponds with an apparent half-life of 2 h 22 min.

The AUC, extrapolated to infinity, was very similar for the three modes of administration, indicating that the total amount absorbed did not differ ($F_{2, 10} = 0·33$; $P > 0·05$).

The absorption rate constants for the three conditions did not differ significantly ($F_{2, 10} = 0·33$; $P > 0·05$); the mean value corresponds with an absorption half-life of 32 min.

There was a wide variation in lag-times, but again no appreciable difference between the modes of administration ($F_{2, 10} = 0·53$; $P > 0·05$); the mean lag-time was 30 min.

The mean maximal concentration and time of maximal concentrations calculated by substituting mean values of the pharmacokinetic parameters in equation (3) and equation (4) were 2·76 mg/l and 1 h 29 min (after lag-time), respectively.

Discussion

Our results show that, in contrast with ketoconazole (van der Meer *et al.*, 1980), the absorption of vibunazole after oral administration is not changed either by enhancing gastric acidity by oral administration of hydrochloric acid or by inhibiting secretion of gastric juice by oral administration of cimetidine (Douglas, 1980), compared with the absorption of vibunazole taken with water.

Since, the apparent elimination rate is very similar for the three modes of administration, the calculated absorption rate constants as well as the extrapolated areas under

the curve are reliable parameters of absorption under the three conditions. The absorption is remarkably uniform with little variation; this suggests that absorption is almost total. The lag-time showed a relatively large variation probably due more to the experimental conditions (fasting) than to variation in dissolution time.

Therefore, unlike ketoconazole, the orally administered antifungal drug vibunazole is very reliably absorbed and this process is not influenced by gastric acidity. This could be an advantage in the oral treatment of fungal infections.

Acknowledgements

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