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# Disposition of Ketoconazole, an Oral Antifungal, in Humans

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The pharmacology of ketoconazole was studied in patients with fungal infections. After administration of 50-, 100-, and 200-mg doses of ketoconazole, there was a linear increase in the area under the curve of serum concentrations; this was not apparent when higher doses of ketoconazole were given. An increase in the area under the curve occurred in patients receiving 200 mg daily who were restudied after 1 to 12 months of therapy. However, normalized area under the curve appeared to decrease after higher doses were administered chronically. The half life ranged from 2.0 to 3.3 h. Peak serum concentrations up to 50 μg/ml were detected in this study, and potentially therapeutic concentrations were detectable up to 26 h after high doses. Ketoconazole penetrated the saliva and inflamed joint fluid and meninges, although variably, and could be demonstrated in some other tissue compartments. In the presence of renal failure, ketoconazole disposition was not altered, whereas in the presence of hepatic insufficiency, an alteration in disposition was suggested. The interactions of ketoconazole and other drugs were studied. Of note, antacids did not significantly affect ketoconazole pharmacokinetics (nor did meals), and ketoconazole and warfarin did not appear to affect the pharmacokinetics of the other.

Ketoconazole is a new, broad-spectrum, orally administered, antifungal agent. The therapeutic efficacy of ketoconazole has been previously reported (7), but scant data on the pharmacokinetics of ketoconazole in patients have been published. We present here the results of our studies of the pharmacokinetics of ketoconazole.

## MATERIALS AND METHODS

**Single-dose studies.** Pharmacokinetic studies were performed in patients upon entry into the ketoconazole therapeutic trial. The first six adult patients received 50, 100, or 200 mg after overnight fasting. The order of these doses was determined by a balanced crossover design. Each dose was administered 48 h after the previous dose. To give 50 mg of ketoconazole, one-half of a scored, 200-mg tablet was dissolved in 60 ml of orange juice; 30 ml of this solution was administered to the patients. Before dosage, a catheter was placed in an antecubital vein and flushed with 3 ml of sterile, normal saline containing 1 U of heparin USP per ml. After the first 3 ml of blood was discarded, 10 ml of blood was collected, and the serum was separated after clotting occurred. Samples were taken before administration of the drug and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h.

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After completion of this study, five additional patients (four adults and one child) were also randomized to the dosage schedule, but in three patients, indwelling intravenous catheters were not used. An additional four patients were studied after they received only the 200-mg dose. Serial sampling as described above was performed in three patients after the first dose of 400 mg. Other patients were studied after initiation of 600 to 1,200 mg of daily therapy. Serum samples were collected at intervals from 0 to 26 h after administration. Four healthy volunteers received a 600-mg dose.

Patients were studied after administrations of 200 mg of ketoconazole and 30 ml of an antacid (Maalox) on empty stomachs after overnight fasts. Others were studied after ingestion of hospital breakfasts and simultaneous administrations of ketoconazole. Four patients received ketoconazole (200 mg) 1 h before eating hospital breakfasts.

**Multiple dose studies.** To examine the possibility of changes in ketoconazole disposition after chronic daily administration, we studied seven patients on nine occasions after administration of ketoconazole (200 mg) for 1 month or more. Other patients were studied months after daily administration of higher doses of ketoconazole (interval ketoconazole pharmacokinetics).

**Special studies.** Two patients with renal failure who were undergoing hemodialysis and one patient with hepatic insufficiency (manifested by recurrent encephalopathy after ingestion of large quantities of protein, clinical evidence of portal hypertension, as well as

serum protein and coagulation abnormalities) were studied after initial doses of 200 mg. The patient with hepatic insufficiency was also studied after the administration of a 400-mg dose.

In addition, patients were studied who had received two to three 200-mg doses daily.

Thirty cerebrospinal fluid (CSF) samples were obtained 30 min to 28 h after a dose. Of seven patients, four had active meningeal disease at the time of therapy (increased leukocytes and protein and decreased glucose). Five joint fluid samples were taken from knees with active coccidioidal arthritis.

In one patient, samples of saliva were collected approximately 0, 1, 2, 4, 6, and 8 h after oral administration of ketoconazole.

**Ketoconazole-warfarin and other interaction studies.** To ascertain whether ketoconazole augments the hypothrombinemia of racemic warfarin as reported with miconazole and warfarin (3), two volunteers were given 7.5- to 15-mg doses of warfarin orally in the evening for 3 weeks. Prothrombin times were determined 13 times during this interval. After a 3-week rest period, the same subjects received the same doses of warfarin as before, plus ketoconazole (200 mg) daily in the morning for 3 weeks. Prothrombin times were determined, and serum ketoconazole concentrations were measured 2 h after the daily dose 13 times during this phase of the study.

Patients receiving other medications for other medical conditions were selected for pharmacokinetic studies to begin a data base in ketoconazole-drug interactions.

**Analysis of ketoconazole.** Concentrations of ketoconazole in serum were determined with an agar well diffusion assay (5). The sensitivity of this assay is ≥0.05 μg/ml. Ketoconazole hydrochloride (Janssen Pharmaceutica) was added to blood group AB, heat-inactivated serum to construct a standard curve for each plate on which serum samples were run. The indicator organism was *Kluyveromyces fragilis* strain 55-1. Values for samples from body fluids other than saliva were obtained from standard curves of ketoconazole diluted in 0.9% saline; for determinations of drug in saliva, normal saliva was used as the diluent. Values for samples from tissue were obtained from standard curves of ketoconazole that had been diluted in a saline suspension of ground tissue from the corresponding site removed from an untreated patient at autopsy.

**Pharmacokinetic calculations and statistics.** The total area under the curve (AUC) (μg.h/ml) for a time interval for serum concentrations of ketoconazole was calculated by the trapezoidal rule (4) and was normalized by dividing AUC by the dose of the drug administered. Assessments for possible nonlinearity in absorption, distribution, or elimination with different doses could then be made.

A paired *t* test and an analysis of variance were used to compare the normalized AUC (NAUC) for 50-, 100-, and 200-mg doses in 10 adult patients. These data were also analyzed with the Mann-Whitney *U* test (8), as were other data with apparent nonnormal distribution (kinetics after 200 mg alone versus 200 mg with meals). The correlation coefficient for the comparison of weight with AUC was calculated.

To assist in visualizing the time course of absorption and elimination, plots of serum concentrations versus time were constructed on semilog paper from the data generated after administration of 200, 400, 600, and 1,200 mg of ketoconazole by using the means for each time period.

## RESULTS

**Comparison of 50-, 100- and 200-mg doses of ketoconazole.** For the majority of patients, the concentrations of ketoconazole peaked between 1 to 2 h after administration. Peaks 3 to 4 h after the dose occurred in some patients. The mean (± standard deviation) peak concentrations for doses of 50, 100, and 200 mg were 1.0 (±0.72), 1.60 (±1.16), and 2.75 (±1.78) μg/ml, respectively. The serum concentration versus the time plot after 200 mg is shown in Fig. 1. The $t_{1/2}$ for the kinetic curve in Fig. 1 is estimated to be 3 h. Although individual patient curves were log linear in this phase, continued absorption, distribution, or elimination, or a combination of these, from a small tissue compartment may have been occurring during this interval, and this estimate may need to be revised when later sampling is done.

The mean AUC was calculated from data from 10 adult patients who received 50, 100, or 200 mg in a randomized fashion (Table 1). NAUC is also given. There was no correlation between weight and AUC after administration of 200 mg (correlation coefficient $r = 0.636$, $P < 0.2$). The range of the weights of the patients was 84 to 251 lb (38.1 to 113.9 kg). The AUC for 200 mg in two patients who were obese were within the AUC ± one standard error of the mean for this group.

Analysis of these data revealed no evidence of nonlinearity (i.e., lack of proportionality between dose and AUC, and no differences in

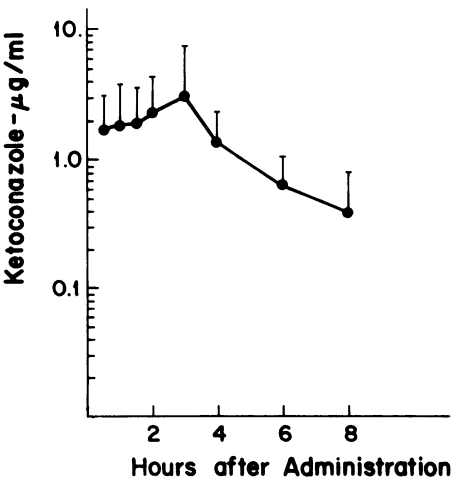


FIG. 1. Administration of 200 mg of ketoconazole to 15 adult patients. Each point represents mean ± standard error of ketoconazole in serum.

TABLE 1. AUC and NAUC in 10 patients receiving the balanced crossover design

| Ketoconazole dose (mg) | Mean serum concn | |
|---|---|---|
| | $AUC_0^8$ ± SE (μg.h/ml) | NAUC ± SE (μg.h/ml per dose in mg) |
| 50 | 3.37 ± 0.83 | 0.067 ± 0.02 |
| 100 | 5.73 ± 1.88 | 0.057 ± 0.01 |
| 200 | 9.70 ± 1.88 | 0.048 ± 0.01 |

NAUC) over the dose range from 50 to 200 mg. In two patients receiving 200 mg of ketoconazole every 12 h and in one receiving 200 mg every 8 h, there was an increase in AUC from 0 to 8 h after dose ($AUC_0^8$) over that found in recipients of 200 mg once daily (Table 2). The increase in $AUC_0^8$ after multiple doses is greater than would be predicted for a drug with an apparent terminal half-life ($t_{1/2}$) of approximately 3 h.

**Kinetics of ketoconazole doses of 400, 600, and 800 mg.** Only three patients received 400 mg of ketoconazole, and two patients received 600 mg in the second phase of the studies. Peak concentrations, AUC, and NAUC are shown in Table 3. Peak concentrations and $AUC_0^8$ did not increase in proportion to the increased dose (cf. Table 1). The kinetics of serum concentrations after 400- and 600-mg doses are shown in Fig. 2 and 3. The four volunteers who received 600 mg had mean concentrations at 2, 4, 8, and 24 h of 7.95 (range, 3.4 to 14.0), 3.99 (2.6 to 5.6), 3.86 (2.3 to 5.3), and 0.14 (0.1 to 0.2) μg/ml, respectively. These kinetics are consistent with those of the more detailed studies (Fig. 3).

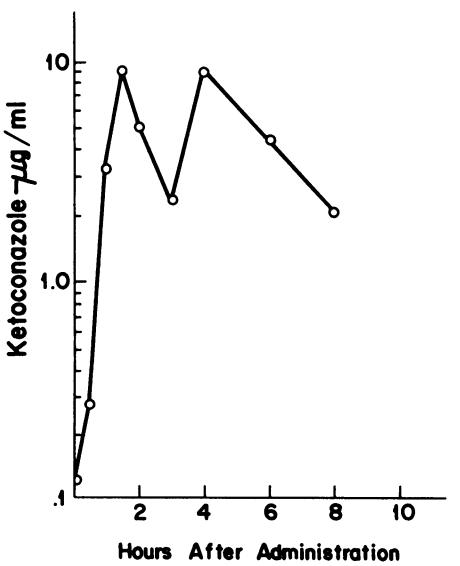


FIG. 2. Administration of 400 mg of ketoconazole to three patients (mean values shown).

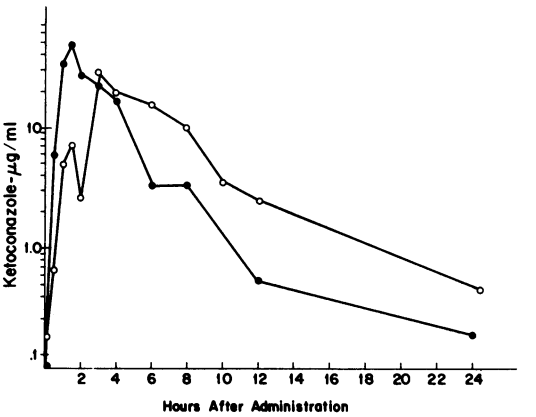


FIG. 3. Administration of 600 mg of ketoconazole to two patients.

AUC, NAUC, and peak concentrations for 400-, 600-, and 800-mg dose administration in two patients in further studies are shown in Table 4. Although not shown in this table, the persistence of detectable (and possibly therapeutic) concentrations long after administrations of the 800-mg dose was noteworthy. Four sera obtained 9 to 15.5 h after a dose averaged 3.34 μg of ketoconazole (range, 1.55 to 5.90) per ml, whereas four sera obtained 24 to 26 h after a dose averaged 2.36 μg/ml (range, 0.20 to 7.75) (cf. late samples in Fig. 1–3). These data would suggest a modest contribution from a small tissue compartment, resulting in a slower, terminal phase of elimination.

Although the number of patients is too few to be certain that there is nonlinearity in oral disposition, this theory is strengthened by the similarities of NAUC for a 200-mg dose for the 3 patients receiving both 200 and 400 mg doses, the patient receiving 200 and 600 mg, and for the 10 patients listed in Table 1.

**Interaction of ketoconazole with Maalox and meals.** The effect of simultaneous administration

TABLE 2. $AUC_0^8$ of ketoconazole in single doses with or without administration of meals or Maalox, or as part of a multiple-dose regimen

| Ketoconazole dose (mg) | Mean $AUC_0^8$ ± SE (μg.h/ml) | No. of patients |
|---|---|---|
| 200, fasting | 9.7 ± 1.88 | 10[a] |
| 200, with Maalox | 5.73 ± 1.92 | 4 |
| 200, with meals | 7.76 ± 2.03 | 7 |
| 200, with meal 1 h later | 14.25 ± 7.43 | 4 |
| 200, twice a day[b] | 23.67 | 2 |
| 200, three times daily[b] | 18.67 | 1 |

[a] From Table 1.

[b] Studied after single dose of 200 mg, 24 to 72 h after initiation of the multiple-dose regimen.

TABLE 3. Pharmacokinetics after 200, 400, or 600 mg of ketoconazole

| Patient | Patient dose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 200 mg | | | 400 mg | | | 600 mg | | |
| | $AUC_0^8$ (μg.h/ml) | $NAUC_0^8$ (μg.h/ml per dose) | Peak concn (μg/ml) | $AUC_0^8$ (μg.h/ml) | $NAUC_0^8$ (μg.h/ml per dose) | Peak concn (μg/ml) | $AUC_0^8$ (μg.h/ml) | $NAUC_0^8$ (μg.h/ml per dose) | Peak concn (μg/ml) |
| 1 | 13.61 | 0.068 | 2.70 | 33.15 | 0.083 | 12.5 | —[a] | — | — |
| 2 | 27.69 | 0.138 | 2.75 | 35.06 | 0.087 | 7.8 | — | — | — |
| 3 | 10.22 | 0.051 | 3.40 | 42.04 | 0.105 | 18.0 | — | — | — |
| 4 | 17.05 | 0.085 | 3.50 | — | — | — | 125.0 | 0.208 | 50 |
| 5 | — | — | — | — | — | — | 107.8 | 0.179 | 30 |

[a] —, Not done.

of Maalox (four patients) or meals (seven patients) with ketoconazole is shown in Table 2. Whereas individual patients showed decreased peak concentrations or a decrease in AUC, the differences do not have statistical significance. The ingestion of a meal 1 h after administration of ketoconazole appeared to have little effect on drug absorption. One patient received 400 mg with a meal and demonstrated an increase in $AUC_0^8$ (56.99 for ketoconazole with a meal versus 33.16 for 400 mg of ketoconazole alone).

**Repeated studies after chronic administration of ketoconazole.** Mean NAUC in the patients restudied on 200-mg doses (seven patients) was significantly higher than initial NAUC for these patients after the first dose of 200 mg of ketoconazole ($P < 0.02$). Average NAUC for the initial 200-mg dose was 0.04 ± 0.01, which is less than half of subsequent NAUC (obtained 1 to 12 months later) of 0.09 ± 0.02.

An increase was also observed in the patient who had a repeat determination after 3 months of administration of a 400-mg daily dose (initial NAUC, 0.08; follow-up NAUC, 0.14).

The repeated pharmacokinetic evaluations at 800 mg are shown in Table 4. AUC for the repeated studies for patients receiving 800 mg was decreased by >45 and 31%, respectively.

**Ketoconazole administration in renal or hepatic failure.** Two patients with renal failure who were undergoing hemodialysis were studied. In these patients, $t_{1/2}$ (1.8 h) was in the same range as that observed in other patients with normal renal function (2.0 to 3.3 h). The clearance of ketoconazole by hemodialysis is probably small relative to endogenous clearance since $t_{1/2}$ and AUC of the compound were not significantly reduced during dialysis (Table 5). Peak concentrations (0.75 and 5.9 μg/ml) were within the range of the values found in patients with normal renal function. Concentrations of ketoconazole in arterial and venous blood samples obtained simultaneously during dialysis were essentially identical, indicating that dialysance of ketoconazole is minimal.

One patient with hepatic insufficiency was also studied (Table 6). The remarkable finding in this patient was the plateau of concentrations after both 200- and 400-mg doses (Fig. 4). This was not observed in any other patient studied; however, the terminal $t_{1/2}$ could not be determined because serum samples were not obtained for a sufficient length of time. It is of interest that there was no evidence of drug accumulation in this patient as determined by the AUC after the first and a subsequent 400-mg dose (Table 6).

**Ketoconazole-drug interaction studies.** Two patients were studied to assess possible drug inter-

TABLE 4. Administration of large doses of ketoconazole (400 to 800 mg) to two patients

| Patient no. | Dose of ketoconazole | $AUC_0^9$ (μg.h/ml) | $AUC_0^5$ (μg.h/ml) | $NAUC_0^9$ (μg.h/ml per dose) | $NAUC_0^5$ (μg.h/ml per dose) | Peak concn (μg/ml) |
|---|---|---|---|---|---|---|
| 1 | 400 | 50.97 | | 0.127 | | 7.15 |
| | 600 | 70.12 | | 0.117 | | 13.50 |
| | 800 | 64.75 | | 0.081 | | 11.50 |
| | 800[a] | 35.82 | | 0.044 | | 4.98 |
| 2 | 400 | | 34.70 | | 0.087 | 10.0 |
| | 800 | | 43.80 | | 0.055 | 27.5 |
| | 800[b] | | 30.25 | | 0.038 | 9.5 |

[a] AUC and NAUC are calculated from 0 to 10 h. Patient had received daily doses of ketoconazole (800 mg) for 4 months.

[b] Patient had received daily doses of ketoconazole (800 mg) for 3 months.

TABLE 5. $AUC_0^6$ and $NAUC_0^6$ of patients with renal failure who were given 200 mg of ketoconazole

| Subject and conditions | $AUC_0^6$ (μg.h/ml) | $NAUC_0^6$ (μg.h/ml per dose) |
|---|---|---|
| Patient no. 1 | 2.77 | 0.013 |
| Patient no. 2 | 15.02 | 0.075 |
| During 4 h of dialysis | 22.74 | 0.114 |
| Patients with normal renal function[a] | 8.04 | 0.040 |

[a] From 15 patients receiving ketoconazole on an empty stomach (mean values shown for comparison).

tients were studied to assess possible drug interactions.

A man with coccidioidal meningitis who had participated in the pharmacokinetics studies and had been given 400 mg of ketoconazole developed focal seizures, for which phenytoin (300 mg daily) was prescribed. His fungal disease subsequently relapsed, and because of inadequate responses to amphotericin and miconazole, treatment with ketoconazole was reinstituted at higher doses of 600 and 1,200 mg. The dosage of phenytoin was continued, and the results of 24-h kinetic studies (Fig. 5) show that peak concentrations, AUC, and NAUC (Table 7) were low compared with those of patients

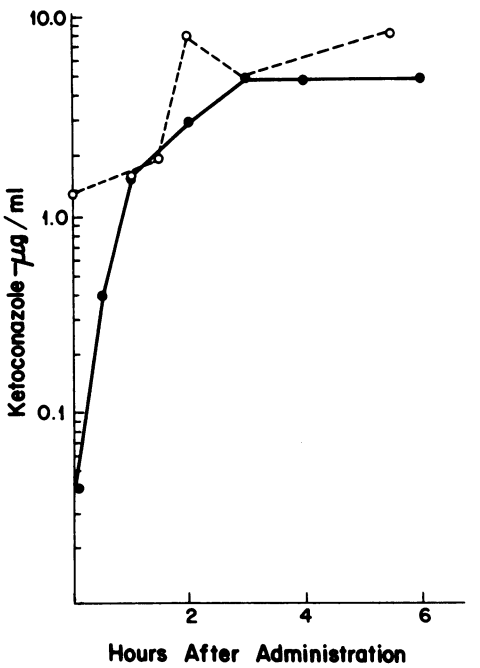


FIG. 4. Administration 200 (●) and 400 mg (○) of ketoconazole to the patient with hepatic insufficiency.

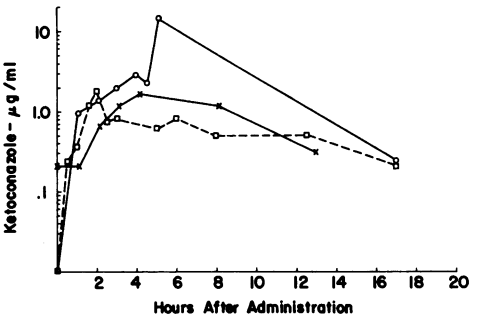


FIG. 5. Repeated administration of ketoconazole in the patient receiving phenytoin (300 mg daily). Symbols: □, 400-mg dose before administration of phenytoin; X, 600 mg after administration of phenytoin; and ○, 1200 mg after administration of phenytoin.

receiving only 400 or 600 mg of ketoconazole. It was interesting that in the serum of this patient, the concentration of ketoconazole peaked later than in recipients of these doses.

Another male patient with coexistent tuberculosis was treated with isoniazid (INH) and rifampin. He was studied after the first 200-mg dose of ketoconazole and then again after administration of 600 mg of rifampin 1 h before 200 mg of ketoconazole. A third study was performed 3 months after starting concurrent ketoconazole, INH, and rifampin. The striking decrease in AUC after 3 months of daily administration of ketoconazole and rifampin (Fig. 6) suggests that rifampin is capable of inducing more rapid metabolic clearance of ketoconazole. The data suggest that this interaction takes some time to develop fully since little, if any, reduction in AUC was evident in the initial study when only a single dose of rifampin was given.

The two volunteers given warfarin and keto-

TABLE 6. Ketoconazole pharmacokinetics in a patient with hepatic dysfunction

| Subject and dose (mg) | Peak concn (μg/ml) | $AUC_0^6$ (μg.h/ml) | $NAUC_0^6$ (μg.h/ml per dose) |
|---|---|---|---|
| Patient with hepatic dysfunction: | | | |
| 200 | 5.0 | 21.91 | 0.110 |
| 400 | 8.3 | 28.20 | 0.070 |
| 400[a] | 4.2 | 17.85 | 0.045 |
| Patients without hepatic failure: | | | |
| 200 (15)[b] | | 8.04 | 0.040 |
| 400 (3)[b] | | 29.59 | 0.076 |

[a] After 2 months of 400 mg daily.

[b] No. of patients shown in parentheses (mean values).

TABLE 7. Ketoconazole-drug interactions

| Patient | Ketoconazole dose (mg) | $AUC_0^8$ (μg.h/ml) | $NAUC_0^8$ (μg.h/ml per dose) |
|---|---|---|---|
| 1 | 400[a] | 5.45 | 0.014 |
| | 600[b] | 8.88 | 0.015 |
| | 1,200[b] | 93.09 | 0.078 |
| 2 | 200 | 17.33 | 0.086 |
| | 200 + 600 mg of rifampin[c] | 9.15 | 0.046 |
| | After 5 mo of 200 + 600 mg of rifampin and 300 mg of INH daily | 2.02 | 0.010 |

[a] Before phenytoin.
[b] Patient also received phenytoin (300 mg daily).
[c] Single dose administration of the two drugs.

conazole showed no hypothrombinemic interaction. The concentrations of ketoconazole 2 h after administration also remained relatively constant (mean, 4.6 μg/ml at the beginning of therapy and 3.0 μg/ml after 1 month of ketoconazole).

**Ketoconazole concentrations in body fluids and tissues.** Twenty-two samples of cerebrospinal fluid (CSF) were collected from four patients with active meningeal disease, and eight samples of CSF were collected from three patients without active meningeal disease. In the patients without active meningeal disease, no ketoconazole was detected (one sample was obtained from a patient receiving 400 mg; seven samples were obtained from the patients receiving 200 mg).

Patients with meningeal disease who were receiving 200 mg of ketoconazole (4 samples collected 60 to 130 min after dosage) had CSF concentrations ranging from 0 to 0.24 μg/ml. The range of CSF concentrations in patients with inflamed meninges who were receiving 400 mg ranged from 0 to 0.85 μg/ml (17 samples collected 60 to 225 min after dosage). Six samples obtained in the 60- to 225-min interval and one obtained 28 h after a dose had no detectable drug. The average CSF concentration of all patients receiving 400 mg was 0.39 μg/ml. There appears to be no significant association between the serum concentration of ketoconazole and CSF concentration at the same sampling times. Three of four patients had evidence of long-standing meningeal disease (>6 months). One patient was treated within the first few months of the onset of meningeal disease; however, there was no significant difference in peak CSF concentrations of ketoconazole in this patient as compared with those of patients who had meningeal disease for longer than 6 months.

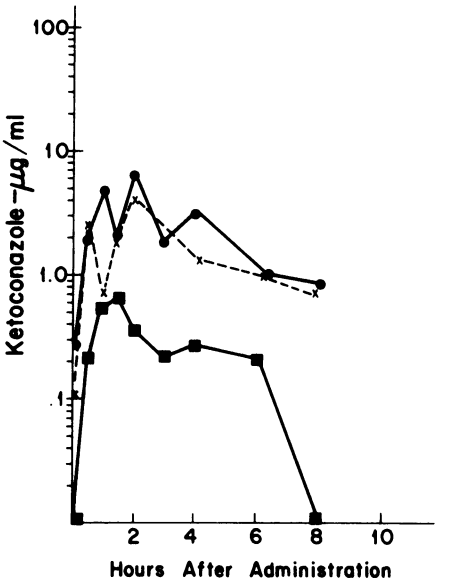


FIG. 6. Ketoconazole interaction with rifampin and INH. Symbols: ○, 200 mg of ketoconazole; X, 200 mg of ketoconazole and 600 mg of rifampin (single dose); and ■, 200 mg of ketoconazole plus 600 mg of rifampin after daily administration of both drugs plus INH for 5 months.

Joint fluid samples obtained approximately 120, 160, 480, and 570 min after the administration of 200 mg of ketoconazole to various patients had ketoconazole concentrations of 0.06, 0.12, 2.50 (simultaneous serum concentration, 2.40 μg/ml), 1.04, and 0.60 μg/ml, respectively. Since saline was used for the standard curve in this assay, the concentration of ketoconazole in the joint fluid, due to the protein binding (2) of this compound in joint fluid, may be underestimated.

Tissue was obtained from one child with coccidioidomycosis of the fifth metacarpophalangeal joint and phalanx at the time of amputation of his phalanx. Ketoconazole was administered 2 h before the collection of samples. Tissue in which concentrations were assayed included uninfected bone, soft tissue, and tendon, and infected bone and skin. The uninfected bone and soft tissue and infected bone had no detectable ketoconazole; the tendon had a ketoconazole concentration of 2.0 μg/ml. The samples of infected skin had a ketoconazole concentration of 10.7 μg/ml.

Saliva samples in the same patient were obtained after administration of 50, 100, and 200 mg. No detectable saliva-ketoconazole concentrations were observed after administration of 50 mg. The concentration in saliva was 0.59 μg/ml 45 min after administration of 100 mg. No detectable drug was found at any other time during

the 8-h sampling period. After a 200-mg dose, ketoconazole concentrations were 2.43 and 0.30 μg/ml 1 and 2 h after administration, respectively. No drug was detected at any other time during the 8-hour sampling.

## DISCUSSION

The analysis of $NAUC_0^8$ demonstrates linearity over the range of 50 to 200 mg (Table 1). NAUC for the 400- and 600-mg doses appeared nonlinear (Table 3). If confirmed, this would suggest a more complete absorption, nonlinear elimination, saturation of a first pass effect, or decreased volume of distribution. To distinguish among these possibilities, an intravenous preparation for determination of clearance, volume of distribution, and absolute bioavailability is needed.

Another important observation was the remarkably increased $AUC_0^8$ for the interval 200-mg kinetic curve when compared with initial AUC for the 200-mg dose. The mechanism of this increase is unknown, and the possibilities are similar to those indicated above. The preliminary interval pharmacokinetic studies after 800 mg suggested an opposite effect for the higher dose.

The double peaks in serum concentration, seen at higher doses of ketoconazole (Fig. 2 and 3), raise the question of enterohepatic circulation or delayed absorption. Multiple daily doses increase the AUC of each dose. Obesity does not appear to affect the pharmacokinetics.

The observation of a 10-fold decrease in peak serum concentration in the patient taking rifampin, INH, and ketoconazole, as well as the reduction of AUC after chronic administration of ketoconazole doses >400 mg daily, suggest that the induction of the cytochrome (P450) hepatic mixed-oxidase system plays an important role in the disposition of the drug and that drugs that affect the P450 system may affect the disposition of ketoconazole. The reduction of AUC after chronic administration of >400 mg ketoconazole daily raises the possibility that the drug itself may induce enzymes which accelerate its disposition. A related imidazole, clotrimazole, has this property (1).

The study of the potential interaction of Maalox and meals with ketoconazole demonstrates the variable effects of meals and Maalox. Workers at Janssen Pharmaceutica have suggested that antacids and cimetidine can decrease the absorption of ketoconazole, resulting in variable serum concentrations of the latter (7). The variable effect of meals and Maalox on our patients probably represents the nonuniform neutralization of stomach acids, which may be less likely in patients studied on a standard dose of cimetidine. Although small depressions in absorption by antacid administration cannot be excluded by our data, major decreases do not appear to occur.

Renal failure did not affect the peak drug concentrations or the elimination $t_{1/2}$ of ketoconazole in two patients studied. Preliminary studies indicate that this drug is extensively metabolized by the liver, and the elimination of unchanged drug and metabolites takes place primarily through the biliary tract (W. Meuldermens, personal communication); only a small amount of unchanged drug is excreted via the kidney.

In the one patient with hepatic insufficiency, serum concentrations remained persistently high without evidence of an elimination phase during the 8-h sampling interval (Fig. 4), which suggested impaired metabolism of the drug. Further studies of patients with hepatic dysfunction would be of interest.

Ketoconazole can penetrate into CSF, but detectable concentrations were seen only in patients with inflamed meninges. The demonstration of significant concentrations of ketoconazole in joint fluid and saliva suggests a role for ketoconazole in the treatment of fungal infections of mouths and joints. The joint fluid data suggests peak levels may be reached later there than in serum. Concentrations of drug in tissue samples may be affected by the vascularity of the tissue and the contribution of the drug in the blood to the assay result. More data concerning the penetration of this drug into body fluids and tissue and correlation with clinical response are needed. Penetration of drug into saliva soon after the tablet was taken cannot be differentiated with certainty from residual oral contamination.

No firm conclusions can be drawn from the patient who was given phenytoin and ketoconazole since this patient may have had a low peak concentration and small AUC after a 400-mg dose before phenytoin was given. Whether the concomitant administration of phenytoin increases the rate of metabolic degradation of ketoconazole is speculative. Studies of hepatic microsomal function as well as the effect of the withdrawal of phenytoin would be of interest. A recent study in rats with relatively short duration of repeated ketoconazole doses did not show hepatic enzyme induction in that species (6).

The clinical utility as well as the limited adverse effects thus far reported with ketoconazole make it likely that this drug will be investigated in a number of deep fungal infections. For this reason, further understanding of the pharmacokinetics of ketoconazole, especially at higher doses, will be very important.

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