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Pharmacokinetics of Itraconazole following Oral Administration to Normal Volunteers

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The pharmacokinetics of itraconazole, an orally effective, broad-spectrum, systemic antifungal agent, were evaluated in five healthy male volunteers. Each subject was studied on days 1 and 15 at the following dosages: 100 mg once daily (regimen A), 200 mg once daily (regimen B), and 200 mg twice daily (regimen C). On each study day, itraconazole was administered with a standardized meal. Plasma samples were collected for 72 h postdose, and 24-h urine specimens were obtained. On day 1 of regimen C, plasma samples were collected following the second dose. Samples were assayed for itraconazole by a sensitive, reverse-phase, high-performance liquid chromatography method. Wide intersubject variations in itraconazole concentration in plasma versus time profiles were observed on all study days. Absorption appeared to be slow, with day 1 mean peak itraconazole concentrations in plasma of 110 ng/ml at 2.8 h (regimen A), 272 ng/ml at 3.0 h (regimen B), and 553 ng/ml at 3.4 h (regimen C). Mean peak itraconazole concentrations in plasma on day 15 were 412 ng/ml at 3.0 h (regimen A), 1,070 ng/ml at 4.4 h (regimen B), and 1,980 ng/ml at 6.0 h (regimen C). The steady state was achieved by day 13. Respective elimination half-lives on days 1 and 15 were 15 and 34 h (regimen A), 20.7, and 36.5 h (regimen B), and 25 and 41.7 h (regimen C), respectively. The areas under the plasma concentration versus time curves (0 to infinity) on day 1 were 1,320 (regimen A), 4,160 (regimen B), and 12,600 ng · h/ml (regimen C) . On day 15, the areas under the plasma concentration versus time curves (0 to 24 h) were 5,330 (regimen A), 15,400 (regimen B), and 39,300 ng · h/ml (regimen C). With the exception of one patient on day 15 of regimen C, itraconazole was not detected in the urine. All data support dose-dependent pharmacokinetic behavior for itraconazole.

Itraconazole (R 51 211), (±)-*cis*-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (Fig. 1), is a new, orally active triazole antifungal agent (5). Itraconazole, which was first synthesized in 1980, demonstrates a broad spectrum of activity against a number of fungal species including dermatophytes, *Malassesia furfur*, *Candida* species, *Aspergillus* species, and *Histoplasma capsulatum* var. *capsulatum* (1). The mechanism of action of itraconazole appears similar to that of ketoconazole, involving inhibition of cell membrane ergosterol synthesis. However, itraconazole differs from ketoconazole in that it demonstrates a high degree of lipophilicity and a lack of endocrine-related side effects.

Itraconazole is an extremely weak base (pK_a = 3.7) which is virtually unionized at physiological pH (2). Since itraconazole is soluble only under extremely acidic conditions, only an oral dosage formulation is currently available for use. The isomers of itraconazole have not yet been separated; thus, in all studies to date the racemic mixture has been evaluated.

The objective of this study was to evaluate the pharmacokinetic behavior of itraconazole following acute and chronic oral administration at daily dosages ranging from 100 to 400 mg.

MATERIALS AND METHODS

Subjects. Five healthy, nonsmoking, adult males (ages, 23 to 42) completed the study. All were within 10% of their ideal weight (65.1 ± 8.8 kg) and had not had a febrile illness within 72 h of entry into the study. Results of all renal, hepatic, and hematological tests were normal. Written, informed consent was obtained from all volunteers, according to institutional and federal policies.

Drug administration. Itraconazole was supplied by Janssen Pharmaceutica (Piscataway, N.J.) as a 50-mg capsule. After an overnight fast, 100 mg of itraconazole was administered with a standardized breakfast. On day 3, this dosage was continued as a morning dose for 13 more days. Following a 2-week washout period, 200 mg of itraconazole was administered daily for 15 days in a similar fashion. After another 2-week washout period, 200 mg of itraconazole was given every 12 h as described above for the once daily dosages. Medication administration was under direct clinical observation on days 1 and 15 at each daily dosage. Outpa-

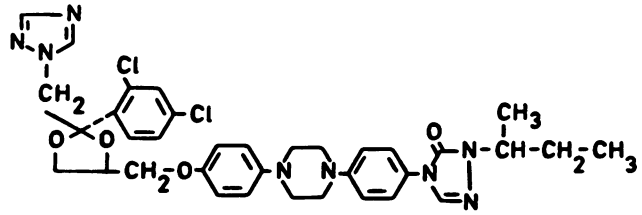

FIG. 1. Structure of itraconazole (R 51 211).

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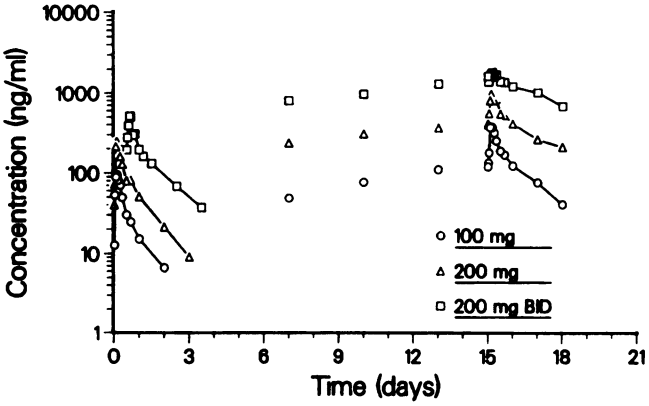

FIG. 2. Observed mean itraconazole concentrations in plasma over time at three daily dosages (n = 5) on days 1 to 15. BID, Dose was administered twice a day.

tient compliance was evaluated by pill counts on each day 15.

Blood and urine sampling. Ten-milliliter blood samples were collected at the following times on days 1 and 15 for each daily dosage: predose (0) and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 h postdose. Additional predose blood samples were collected on days 7, 10, and 13; and 24-h urine collections were obtained on days 1 and 15 for each regimen. Following refrigerated centrifugation, separated plasma samples were frozen at −70°C and stored until analysis. Urine samples were similarly frozen and stored.

High-performance liquid chromatography assay. Itraconazole concentrations were determined by a reverse-phase, high-performance liquid chromatography technique described by Woestenborghs and co-workers (6). Samples were spiked with internal standard (R 51 012), buffered to pH 7.8 with 0.05 M phosphate buffer, and extracted twice with heptane-isoamyl alcohol (98.5:1.5; vol/vol). The organic phase was back-extracted with 0.05 M sulfuric acid and removed after centrifugation. The remaining acidic phase was made alkaline with concentrated ammonia (pH 9) and reextracted twice with the same heptane-isoamyl alcohol mixture. The combined organic layers were evaporated to dryness under nitrogen. The overall extraction yield was 71.5 ± 2.3%. The extraction residues were redissolved in 100 μl of elution solvent, and 40-μl portions were injected onto a 5-μm column (15 cm by 2.1 mm; RSil C18HL; Alltech Europe). The elution system consisted of 0.5% diethylamine in water-acetonitrile (40:60) pumped at a flow rate of 0.5 ml/min. UV A_{293} was monitored. Retention times for itraconazole and R 51 012 were 4.3 and 5.8 min, respectively. The sensitivity of this method was 1 ng/ml, with a coefficient of variation of 4.1 ± 1.6 over the concentration range of 10 to 1,000 ng/ml.

Pharmacokinetic analysis. The individual concentration (C) in plasma versus time (t) data were evaluated by linear regression analysis to yield the specific terminal-phase elimination rate constant (k_{el}) for each patient on each study day. Elimination half-life ($t_{1/2}$) values were calculated by the following equation: $t_{1/2} = 0.693/k_{el}$. The area under the concentration-time curve (AUC) from zero to infinity ($AUC_{0-\infty}$) for day 1 was calculated by the linear trapezoidal method up to 72 h and extrapolated to infinity by using the terminal C divided by k_{el}. The area under the curve at steady state from 0 to 24 h (AUC_{0-24}) for day 15 was calculated by trapezoidal summation. The area under the curve for day 1

TABLE 1. Mean C in plasma for five volunteers after initial oral dosing of itraconazole at three daily dosages (day 1)

Dose	Mean C ± SD (ng/ml) after the following times (h):											
	0.5	1	2	3	4	6	8	12	16	24	48	72
100 mg/day	12.6 ± 21.6	52.6 ± 61.4	88.3 ± 59.5	94.6 ± 52.2	80.6 ± 38.2	69.4 ± 31.2	49.1 ± 19.4	29.8 ± 12.6	24.3 ± 11.3	15.0 ± 8.8	6.6 ± 2.8	—[a]
200 mg/day	39.8 ± 22.2	72.0 ± 55.6	213 ± 128	248 ± 108	244 ± 89.8	159 ± 78.4	128 ± 65.6	79.2 ± 33.6	80.8 ± 35.3	50.2 ± 30.5	21.1 ± 4.6	9.0 ± 10.3
200 mg twice a day[b]	193 ± 163	275 ± 156	388 ± 149	508 ± 189	503 ± 200	296 ± 74.5	306 ± 96.3	195 ± 68.0	160 ± 65.6	130 ± 60.3	67.9 ± 44.3	36.9 ± 32.1

[a] —, Levels below lowest measurable concentration.
[b] After the second dose.

TABLE 2. Mean C for five volunteers after chronic oral dosing of intraconazole at three daily dosages (day 15)

Dose	Mean C ± SD (ng/ml) after the following times (h):											
	0.5	1	2	3	4	6	8	12	16	24	48	72
100 mg/day	135 ± 27.6	280 ± 68.8	376 ± 73.3	385 ± 95.2	378 ± 116	323 ± 122	255 ± 97.7	190 ± 65.8	170 ± 52.4	124 ± 47.7	77.2 ± 37.6	41.1 ± 23.7
200 mg/day	407 ± 207	564 ± 260	820 ± 331	990 ± 383	1,028 ± 447	822 ± 373	864 ± 560	557 ± 192	535 ± 251	419 ± 179	268 ± 122	214 ± 127
200 mg twice a day	1,420 ± 290	1,450 ± 420	1,640 ± 594	1,730 ± 543	1,820 ± 572	1,660 ± 564	1,720 ± 293	1,420 ± 378	1,390 ± 394	1,230 ± 286	1,040 ± 293	698 ± 110

TABLE 3. Mean trough itraconazole C in plasma observed with chronic dosing (n = 5)

Dose	Mean C ± SD (ng/ml) on the following days:				
	2	7	10	13	15
100 mg/day[a]	15.0 ± 8.8	48.5 ± 24.5	76.7 ± 29.1	111 ± 39.4	124 ± 47.7
200 mg/day[a]	50.2 ± 30.5	287 ± 53.1	310 ± 123	371 ± 158	419 ± 180
200 mg twice a day[b]	130 ± 60.3	807 ± 190	980 ± 358	1,330 ± 390	1,420 ± 378

[a] At 24 h postdose.
[b] At 12 h postdose.

of the 200-mg twice daily dosage was determined by adding the data from the 200-mg single dose evaluation for the period 0 to 12 h to the data observed over 12 h following the second dose of itraconazole. On day 15 of the 200-mg twice daily dosage, the AUC_{0-24} was determined by doubling the AUC for the period from 0 to 12 h (AUC_{0-12}), thus correcting for the failure to administer the second 200-mg dosage on that day. Since no intravenous formulation was available, the absolute bioavailability of itraconazole administered orally is unknown. Therefore, the apparent oral clearance (CL/f) was calculated from the data obtained after oral dosing by using the following equations: CL/f = dose/$AUC_{0-\infty}$ (day 1) or CL/f = dose/AUC_{0-24} (day 15), where f is the fraction of orally administered drug reaching systemic circulation (bioavailability).

Statistical analysis. Repeated measures analysis of variance and the Wilcoxon signed rank test were used to evaluate for significant differences between observed parameters among dosages and within dosages over time. A P value of <0.05 was considered to be significant. All data are reported as means ± standard deviations.

RESULTS

Wide intersubject variations in itraconazole concentration in plasma versus time profiles were observed on all study days (Tables 1 and 2). The mean (± standard deviation) peak itraconazole concentration in plasma (C_{max}) on day 1 of the 100-mg dose per day was 110 ± 57.5 ng/ml, on day 1 of the 200-mg dose per day it was 272 ± 81.2 ng/ml, and following the second dose on day 1 of the 200-mg dose twice a day it was 553 ± 179 ng/ml; the values were observed at 2.8 ± 1.1, 3.0 ± 0.7, and 3.4 ± 0.5 h, respectively (T_{max}). Significant accumulation was observed with chronic dosing, as shown by increasing trough concentrations in plasma on days 7, 10, 13, and 15 (Table 3). Figure 2 illustrates the mean C versus time profiles observed over the 15-day study period for each dose. Evaluation of these data demonstrated no statistical difference between the mean trough concentrations on days 13 and 15, suggesting that by day 13 the steady state was achieved. The mean observed C_{max}s on day 15 were 412 ± 79.5 ng/ml (100 mg per day), 1,070 ± 499 ng/ml (200 mg per day), and 1,980 ± 508 ng/ml (200 mg twice a day).

Interestingly, a second peak was observed at approximately 8 h postdose in all five subjects on day 15 and one subject on day 1 following 200 mg given twice daily and in one subject on day 15 following 200 mg given once daily. However, these values were not found to be statistically different from concentrations observed at 6 and 12 h postdose, probably because of the large standard deviations observed at these times. The k_{el} values were consistently smaller on day 15 compared with those on day 1 for each dosage regimen, and calculated $t_{1/2}$ values increased for each daily dosage evaluated between days 1 and 15 (Table 4). The mean AUC (in nanogram · hours per milliliter) on day 1 ($AUC_{0-\infty}$) and the mean AUC at steady state (AUC_{0-24}) on day 15 for each dosage are illustrated in Table 4, along with the mean calculated CL/f (in liters per hour per kilogram).

With the exception of one subject who excreted a total of 9.4 μg per 24 h on day 15 of a regimen of 200 mg of itraconazole twice daily, itraconazole was not detected in the urine samples submitted for assay.

DISCUSSION

Itraconazole pharmacokinetics have been reported in a number of animal species (2). A marked enhancement of oral absorption of itraconazole when given with a meal, extensive tissue distribution, and multiphasic elimination have been described. Also, proportionately increased mean

TABLE 4. Means of pharmacokinetic parameters following itraconazole administration (n = 5)

Dose and day	C_{max} (ng/ml)	T_{max} (h)	k_{el} (h^{-1})	$t_{1/2}$ (h)[a]	$AUC_{0-\infty}$ (ng · h/ml)	AUC_{0-24} (ng · h/ml)	CL/f (liter/h per kg)
100 mg/day							
Day 1	110 ± 57.5	2.8 ± 1.1	0.0557 ± 0.0290	15.0 ± 5.7	1,320 ± 651		1.511 ± 0.863
Day 15	412 ± 79.5	3.0 ± 1.2	0.0216 ± 0.0062	34.0 ± 8.5[b]		5,330 ± 1,470[b]	0.308 ± 0.073[b]
200 mg/day							
Day 1	272 ± 81.2	3.0 ± 0.7	0.0375 ± 0.0120	20.7 ± 9.3	4,160 ± 1,949		0.937 ± 0.587
Day 15	1,070 ± 499	4.4 ± 2.1	0.0192 ± 0.0024	36.5 ± 4.3[b]		15,400 ± 6,880[b]	0.233 ± 0.087[b]
200 mg twice a day							
Day 1	553 ± 179[c]	3.4 ± 0.5[c]	0.0314 ± 0.0120	25.0 ± 10.2	12,600 ± 4,598		0.533 ± 0.138
Day 15	1,980 ± 508	6.0 ± 2.0	0.0178 ± 0.0061	41.7 ± 10.0		39,300 ± 9,970[b]	0.167 ± 0.049[b]

[a] Values are harmonic mean.
[b] Values were statistically different from those on day 1.
[c] Following the second dose.

steady-state levels with increasing dosage, suggesting linear kinetics, have been observed. A large number of itraconazole metabolites with minimal antifungal activities exist and are primarily excreted in the bile. Itraconazole does not appear to be eliminated unchanged in the urine.

Limited pharmacokinetic data exist for itraconazole in humans (2). As reported in animal studies, itraconazole absorption in human volunteers is improved when the oral capsules are given with food rather than in a fasting state. However, absolute bioavailability analysis is not currently possible in the absence of an intravenous product. Extensive tissue binding has been observed after a single 200-mg dose in women undergoing hysterectomy (4).

Our results demonstrate a broad range of itraconazole concentrations in plasma following oral doses of 100 mg per day. Similar variances were observed following doses of 200 mg per day and 200 mg twice a day, the dosage commonly used in clinical trials of systemic itraconazole therapy. Recognizing the effect of food on absorption, all subjects received their dosages with a standardized meal. The second peaks observed with a dose of 200 mg twice daily may be representative of enterohepatic recirculation of unchanged itraconazole. This has not been studied carefully, but it has been demonstrated in rats (2).

Heykants and co-workers (2) have reported that oral absorption and bioavailability of itraconazole are a function of dose. After oral doses of 50, 100, and 200 mg, increases in the AUC and C_{max} were nonlinear, suggesting a saturation of the first-pass metabolism process in the liver. Our findings support this nonlinearity following both single and chronic dosing at 100, 200, and 400 mg per day. The mean C_{max} after a dose of 200 mg per day was 147% higher than the C_{max} after a dose of 100 mg per day on day 1 and 160% higher on day 15. However, this disproportionate increase in mean C_{max} was not observed between doses of 200 mg per day and 200 mg twice a day, possibly because of the twice daily dosages rather than a single 400-mg dose or the saturation of some hepatic metabolic pathway at dosages lower than 200 mg. The mean AUC did, however, consistently show three- to fourfold increases for each dosage evaluated between days 1 and 15, which is characteristic of nonlinear pharmacokinetic behavior.

In addition to the dose dependency of bioavailability described above, we observed significant changes in the pharmacokinetic parameters of k_{el} and CL/f from days 1 to 15 at each dosage regimen studied. Over time, all subjects demonstrated reductions in k_{el} of 43 to 61% and reductions in CL/f of 69 to 80%. Thus, itraconazole hepatic metabolism may be a saturable process which can easily be overcome at the dosages used clinically.

The wide variability in itraconazole concentrations following oral administration was not surprising. Similar variability has been reported with the oral administration of ketoconazole in normal volunteers (3).

In retrospect, the design of this study might have been improved. We used sequential dosage escalation for each subject, separated by a 2-week washout period between regimens. We do not know whether our results would have been similar if the dosages had been assigned randomly, but we doubt that significant differences would have been observed. In addition, we administered 200 mg twice daily rather than 400 mg as a single daily dose. This dosing scheme required alternative data manipulation, as outlined above, in order to calculate the desired pharmacokinetic parameters for this regimen.

In summary, several statements regarding itraconazole pharmacokinetics can be made. (i) Itraconazole demonstrates dose dependency, (ii) the concentrations in plasma observed with chronic dosing (steady state) cannot be predicted from initial oral dosing, and (iii) the route of elimination does not appear to be renal. Further pharmacokinetic analysis of itraconazole will be needed in order to characterize fully the behavior of this new antifungal agent in patient populations.

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