

Pharmacokinetics and Bioavailability of Fluconazole in Two Groups of Males with Human Immunodeficiency Virus (HIV) Infection Compared with Those in a Group of Males without HIV Infection

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Fluconazole pharmacokinetics, including absolute bioavailability, were determined for one group of controls ($n = 10$) and two groups of people with human immunodeficiency virus (HIV) infection (those with CD4⁺ T-cell counts of less than [$n = 4$] or greater than [$n = 9$] 200 cells per mm³). Twenty subjects received four doses of fluconazole; three doses were oral (50, 100, and 400 mg), and one dose was intravenous (either 50, 100, or 400 mg). The other three subjects received one or two doses. The groups were comparable in terms of the weight, body mass index, and estimated creatinine clearance of the subjects, but the people with HIV infection were older. Pharmacokinetic parameters indicated linearity in all subjects; the area under the plasma concentration-time curve and the maximum concentration increased in proportion to the dose. The fraction of an oral dose of fluconazole absorbed approximated unity in all three groups of subjects. The mean (\pm standard deviation) plasma clearance of fluconazole was lowest in the group of subjects with low CD4⁺ T-cell counts; the value for this group was 0.74 ± 0.19 liter/h, compared with 0.97 ± 0.19 liter/h in the group with HIV infection and CD4⁺ T-cell counts of greater than 200 cells/mm³ and 1.18 ± 0.23 liter/h in the group of control subjects ($P < 0.05$). The volume of distribution was lower in those with HIV infection ($P = 0.04$, corrected for weight). The half-life was longest in people with HIV infection and low CD4⁺ T-cell counts ($P = 0.01$). This study has shown that some differences do exist between the pharmacokinetics of fluconazole in people with HIV infection and those in noninfected controls.

Fluconazole, a bis-triazole drug, is useful for the treatment and prophylaxis of superficial and systematic fungal infections, which predominantly affect immunocompromised individuals (14, 15). Such infections, in particular candidiasis and cryptococcal meningitis, are common in people infected with the human immunodeficiency virus (HIV), especially as immune function deteriorates (17). Specific pharmacokinetic properties contribute to the therapeutic utility of fluconazole (9). For example, a low level of protein binding allows high concentrations of drug to cross the blood-brain barrier, making it useful for the treatment of central nervous system infections, and a long half-life enables administration only once or twice daily.

Despite widespread use of fluconazole in the treatment and prophylaxis of these fungal infections in people with HIV infection, dosage regimens have been designed on the basis of pharmacokinetic data derived from studies with healthy subjects (9). There are a number of reasons for examining the pharmacokinetics of fluconazole in people with HIV infection, a group likely to receive the drug therapeutically, to determine whether individualization of the dosage could be used to optimize therapy.

There have been suggestions that the pharmacokinetics of ketoconazole, another imidazole antifungal drug, may be dose dependent (8). Recently, similar suggestions have been made about the pharmacokinetics of another imidazole, itraconazole (2). Nonlinear pharmacokinetics make accurate dosage predic-

tion difficult, since concentrations in plasma increase disproportionately with dose.

Since HIV infection can affect the physiology of many organ systems (4, 12), changes in drug disposition in this group could occur, indicating a need for revision of dosage regimens. To date, changes in the disposition of some substances, including folic acid (16) and clindamycin (13), have been reported. It has been reported that the absorption of ketoconazole is decreased in the presence of a high gastrointestinal pH (3, 8, 20), a condition which can occur in people with HIV infection because of achlorhydria, although this does not appear to occur with fluconazole (3).

One paper described the bioavailability (of a tablet formulation) and pharmacokinetics of fluconazole in people with AIDS (11). Single 100-mg intravenous and oral doses of fluconazole were administered. Pharmacokinetic parameters were compared and were found to be similar to those obtained from population data from previous studies with healthy subjects (historical controls). A concurrent control group was not included. Data from another recent pharmacokinetic study indicated that fluconazole clearance was lower in AIDS patients than in healthy volunteers following administration of single 100-mg intravenous dose of fluconazole (22). A comprehensive study, involving administration of intravenous and oral doses of different sizes to people with HIV infection and to concurrent control subjects, was warranted to address unresolved issues about the disposition of fluconazole in an identifiable group of people likely to receive the drug as therapy.

The aims of this study were therefore to (i) investigate the pharmacokinetics of fluconazole in people with HIV infection at different doses to determine any nonlinearities in the dis-

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position of the drug, (ii) determine the absolute bioavailability of three different doses of fluconazole in people with HIV infection, (iii) evaluate any changes in the pharmacokinetic parameters of fluconazole with different stages of HIV infection, and (iv) compare these parameters with those obtained for a concurrent control group without HIV infection.

MATERIALS AND METHODS

Subjects and study design. The pharmacokinetic parameters of fluconazole, including the absolute bioavailability of the commercially available capsule formulation (Diflucan; Pfizer Pty Ltd), were determined for three different subject groups. Group A consisted of volunteers with HIV infection and a CD4⁺ T-cell count of less than 200 cells per mm³. Group B consisted of volunteers with HIV infection and a CD4⁺ T-cell count of greater than 200 cells per mm³. Group C consisted of volunteers without HIV infection.

The CD4⁺ T-cell count was chosen as a marker of disease progression to differentiate two groups at different stages of HIV infection. It is generally thought that those with CD4⁺ T-cell counts of lower than 200 cells per mm³ are at higher risk of opportunistic infection. This surrogate marker of disease progression is commonly used in therapeutics (e.g., for decisions about commencement of or changes to antiretroviral therapy).

Inclusion in the study was restricted to males between the ages of 18 and 50 years with a body mass index {weight [kilograms]/(height [meters])²} within the range of 18 to 26 (1). Subjects were judged to be fit for participation on the basis of a normal physical examination and clinical chemistry test results, including liver function tests (acceptable if less than twice the normal ranges, i.e., <60 IU of gamma glutamyltransferase and alanine aminotransferase), full blood count (acceptable if all hematological parameters were within the normal quoted hospital ranges), and serum creatinine (acceptable if creatinine clearance, estimated from serum creatinine concentration by the formula of Cockcroft and Gault formula [7], was greater than 3 liters/h). Liver function tests were repeated at the conclusion of the study. Volunteers in group C had an HIV screen, with full counseling, to ensure that they had not been exposed to the virus. CD4⁺ T-cell counts were determined for all subjects in groups A and B before the study was begun.

The study protocol was approved by the Research Ethics Committee of St. Vincent's Hospital, Darlinghurst, Australia. Written informed consent was obtained from each subject prior to participation.

Each subject was scheduled to receive four separate doses of fluconazole (Diflucan); three doses were oral (one 50-mg capsule, one 100-mg capsule, and four 100-mg capsules), and one dose was intravenous. The size of the intravenous dose (either 50, 100, or 400 mg) that a subject received was randomly allocated within each group by using a random number generator on a calculator. The order of dosing (intravenous or oral) and the order of the oral doses were similarly randomly allocated. These random dosing sequences were drawn up for each group before the study commenced, and subjects were sequentially assigned a number (e.g., A1 and A2, etc.) upon entry into the study.

The intravenous doses were administered at a constant infusion rate of 200 mg/h (i.e., over 0.25, 0.5, or 2 h, depending upon the dose). The infusion bottle(s) and all equipment used for administration were weighed before and after dose administration to calculate the exact dose given. The time between each dose was at least 2 weeks to ensure an adequate washout period.

All subjects fasted (no food or fluid) from 2200 on the day prior to drug administration. An indwelling venous cannula was sited on the day of drug administration (in the arm opposite to that used for the infusion when the subject was to receive fluconazole intravenously). One venous blood sample was taken prior to dosing (to ensure that no drug or interfering substance was present initially), and then 5-ml samples were collected at approximately 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 10 h after oral dosing, or after commencement of the infusion, from the indwelling cannula. Blood samples (5 ml) were subsequently collected by individual venipuncture at 24, 32, 48, 72, 96, 120, and 168 h after dosing. All samples were collected into vacuum tubes containing EDTA, without a gel separator layer (Vacutainer; Becton Dickinson, Sydney, Australia), and centrifuged for 10 min prior to harvest of the plasma. The plasma samples remained frozen at -20°C until the time of analysis.

The collection of urine was optional. Those volunteers agreeing to participate in this part of the study were asked to empty the bladder immediately prior to drug administration. An aliquot of this sample was collected to ensure that no drug or interfering substance was present initially. Individual void collections were made during the first 10 h after dose administration, with 24-h collections carried out for the remainder of the week. The sample volumes and voiding times were accurately recorded.

Determination of fluconazole concentration. Concentrations of fluconazole in plasma and urine samples were determined by using a gas-liquid chromatographic method (10), with the following modifications. The internal standard used was another triazole, UK 48134 (Pfizer Central Research, Sandwich, United Kingdom), and the gas-liquid chromatograph used was a model 3400 from Varian Instruments (Frenchs Forest, New South Wales, Australia). The column was DB-5 (15 m by 0.53 mm [internal diameter] by 1.5 μm) (J&W Scientific,

Folsom, Calif.). The oven temperature was 200°C, the injector temperature was 260°C, and the detector temperature was 285°C. The makeup gas flow rate was 175 ml/min, with a linear carrier gas (nitrogen) velocity of 45 cm/s. The volume of sample injected was 3.0 μl, and the split injection mode was used, with a split ratio of 20:1.

To 500-μl samples of plasma, in screw cap glass tubes, were added 500 μl of carbonate buffer (pH 9.0), the internal standard, and 2.0 ml of chloroform. The mixture was shaken for 10 min and then centrifuged for 10 min at 3,000 rpm (Clements GS 200 centrifuge). The upper phase (inorganic) was removed and discarded, and the remaining organic phase was transferred to a glass centrifuge tube and evaporated to dryness at a temperature of 38°C. Samples were resuspended by addition of a drop of chloroform followed by 200 μl of methanol and then vortexed before being transferred to autosampler vials for injection. The retention times of fluconazole and the internal standard were 2.4 and 4.3 min, respectively.

The recovery of fluconazole by use of this modified method was 89, 89, and 91% at concentrations of 0.5, 2, and 10 mg/liter, respectively. The recovery of the internal standard was 88%. The limit of quantitation of the assay was 0.1 mg/liter. Within-run coefficients of variation were less than 6% at plasma drug concentrations of between 0.5 and 10 mg/liter ($n = 3$ at each of four concentrations). Two standard curves were used for fluconazole concentrations of 0.2 to 2 mg/liter and 2 to 20 mg/liter; the amounts of internal standard added were 0.8 and 8 μg, respectively. Concentrations of fluconazole in the study samples were calculated from the peak area ratios (fluconazole to internal standard) and interpolation from a freshly extracted standard curve.

The following criteria were used to determine whether an assay run was accepted: a coefficient of determination (r^2) of greater than 0.98 and two of three quality control samples (concentrations of 0.8 or 8 mg/liter, depending on the standard curve) within ±10% of the nominal value. For a concentration result to be accepted, the coefficient of variation of two duplicate extractions had to be less than 10%. Samples were reassayed if any criteria were not satisfied.

Pharmacokinetic analysis. Nonlinear least-squares analyses were used to fit single-exponential elimination equations to the plasma concentration-time data (each point weighted with the reciprocal of concentration squared) by using Minim (version 2.0) on a Macintosh computer. A single-exponential elimination equation was chosen in preference to a biexponential elimination equation on the basis of Akaike's information criteria (21). The information criteria were lower for the single-exponential fits, indicating that nothing was added to the model by inclusion of further exponentials. Most previous studies have used single-exponential equations to describe elimination (for a review, see reference 9). One group has used biexponential equations (11), but the estimated half-life from the central compartment of the model was less than 1/4 h (mean intercompartmental clearance of 85 liters/h and mean volume of central compartment of 25 liters after intravenous dosing), compared with a terminal elimination half-life of around 40 h. This rapid phase would be very hard to model.

Following intravenous dosing, the parameters of the equation $C = A \cdot e^{-k \cdot t}$, where C is the plasma fluconazole concentration measured at time t after the end of the intravenous infusion and k is the elimination rate constant, were estimated. A first-order input was used with the following single-exponential elimination to describe disposition after oral dosing: $C = A \cdot e^{-k \cdot t} - B \cdot e^{-k_a \cdot t}$, where C is the plasma fluconazole concentration measured at time t after the oral dose, k is the elimination rate constant, and k_a is the absorption rate constant. Estimations of half-life ($t_{1/2}$) were obtained from the fitted equation $t_{1/2} = \ln 2/k$. Areas under the plasma concentration-time curves (AUCs) and areas under the first moments of the curves (AUMCs) were obtained from the plasma concentration-time data by using the linear trapezoidal rule, with an extrapolation to time infinity.

Noncompartmental pharmacokinetic parameters of fluconazole were characterized. The absolute clearance (CL) of fluconazole after an intravenous dose (D_{iv}) was calculated from the equation $CL = D_{iv}/AUC_{iv}$. The volume of distribution at steady state (V_{ss}) was estimated from the equation $V_{ss} = D_{iv} \cdot AUMC_{iv}/AUC_{iv}^2$. The renal clearance (CL_R) was calculated from the equation $CL_R = C_{UR} \cdot V_{UR}/\delta \cdot C_{mdpt}$, where C_{UR} is the fluconazole concentration in urine, V_{UR} is the volume of urine collected over the time interval δ , and C_{mdpt} is the plasma fluconazole concentration at the time closest to the midpoint of the urine collection interval.

The maximum concentration after oral dosing and the time to achieve this concentration were obtained from inspection of the plasma concentration-time data.

The fraction of an oral dose of fluconazole absorbed (F) was calculated from the equation $F = D_{iv} \cdot AUC_{or}/D_{or} \cdot AUC_{iv}$, where D_{iv} and D_{or} are the doses and AUC_{iv} and AUC_{or} are the AUCs following intravenous and oral dosing, respectively. This fraction was calculated for each subject from the data obtained after administration of the equivalent oral and intravenous doses.

Statistical analysis. Data are expressed as mean ± standard deviation, except for discontinuous data (time to maximum concentration), for which median values (and range) are shown. Analysis of variance was used to compare the demographics of the groups. The linearity of the pharmacokinetics of fluconazole was assessed by linear regression of the AUC against dose. The correlation of maximum concentration after oral dosing and dose was determined. The half-lives at different doses in each of the three groups of subjects were also compared by using analysis of variance. Bioavailability parameters (fraction of an oral dose

TABLE 1. Demographics of subjects^a

Group ^b and subject	Age (yr)	Wt (kg)	Body surface area (kg/m ²)	Creatinine clearance (liters/h)	Other medication(s) ^c	CD4 ⁺ T-cell count (cells/mm ³)
Group A						
A1	37	72	23	6.3	ddI, CO-TRI, Flucloxacillin, Diclofenac	108
A2	25	76	22	8.0	Diazepam	96
A3	34	77	24	6.1	CO-TRI	12
A4	50	61	20	4.8	ZDV, ACYC, CO-TRI	156
Mean (±SD)	37 (±10)*	72 (±7)†	22 (±2)**	6.3 (±1.3)††		
Group B						
B1	35	61	20	8.3		504
B2	50	80	25	5.3		325
B3	35	77	24	6.6	ZDV, CO-TRI, interferon	290
B4	31	65	21	7.3	ZDV	290
B5	46	70	23	5.5	ZDV, ddC	384
B6	29	68	19	5.9	ZDV, CO-TRI, ACYC	224
B7	46	61	20	5.6	ZDV, ACYC	551
B8	38	77	23	5.7	ZDV, ddC, ACYC, NITRAZ, RANIT	418
B9	30	62	20	6.4	ZDV	299
Mean (±SD)	38 (±8)*	69 (±7)†	22 (±2)**	6.3 (±1.0)††		
Group C						
C1	20	85	25	6.1		
C2	21	80	24	5.4		
C3	21	72	23	8.0		
C4	30	73	23	6.7		
C5	45	70	23	5.7		
C6	21	78	25	7.2		
C7	22	88	24	8.4		
C8	21	92	26	7.4		
C9	22	70	24	5.9		
C10	18	62	20	8.2		
Mean (±SD)	24 (±8)*	77 (±9)†	24 (±2)**	6.9 (±1.1)††		

^a Analysis of variance: *, $P = 0.0042$; †, $P = 0.13$; **, $P = 0.07$; ††, $P = 0.43$.

^b Group A, subjects with HIV infection and with CD4⁺ T-cell counts of <200 cells per mm³; group B, subjects with HIV infection and with CD4⁺ T-cell counts of >200 cells per mm³; group C, subjects without HIV infection.

^c ddI, didanosine; CO-TRI, co-trimoxazole; ZDV, zidovudine; ACYC, acyclovir; ddC, dideoxycytidine; NITRAZ, nitrazepam; RANIT, ranitidine.

absorbed, maximum concentration, and time to maximum concentration) were compared by analysis of variance for the three groups of subjects and at the three different doses to investigate any differences in absorption either with HIV infection at different stages or with fluconazole dose. The null hypothesis that there is no difference in the pharmacokinetics of fluconazole in people with HIV at two different stages of infection and in noninfected individuals was tested by comparing total clearance, renal clearance, volume of distribution, and half-life estimates between the three groups by using analysis of variance.

Correlation coefficients were determined by linear regression analyses, except for the correlation between maximum concentration and dose, which was determined by using Spearman's rank order correlation. One-factor analyses of variance were performed with the Statview package on a Macintosh computer. Comparisons of pairs of groups were performed by using unpaired Student's *t* tests. Differences were considered statistically significant if $P < 0.05$.

RESULTS

The demographics of the subjects in the three groups are shown in Table 1. Weight, body mass index, and creatinine clearance were similar for all three groups ($P > 0.05$). Subjects in the two groups with HIV infection were significantly older than those without infection ($P < 0.05$ for group A versus group C and for group B versus group C), but there were no significant differences in the mean ages of the subjects within these two groups ($P > 0.05$ for group A versus group B). Most subjects in groups A and B were taking a range of other medications, which are also shown in Table 1.

Investigation of nonlinearities in fluconazole pharmacokinetics. There was no evidence of nonlinearities in the disposition of fluconazole in any subject group. The AUCs following intravenous doses of fluconazole increased in proportion to dose in all three groups of subjects ($r = 0.931$; $P = 0.0001$). Indeed, the AUCs following all doses, oral and intravenous, increased in proportion to dose (Fig. 1) ($r = 0.926$; $P = 0.0001$). The maximum concentrations after oral dosing also increased proportionally with dose (Fig. 2) ($r = 0.958$, $P = 0.0001$). There were no trends in any subject for the elimination half-life of fluconazole to change with dose.

Absorption of oral fluconazole. There were no significant differences in bioavailability parameters between the groups. The mean fraction of an oral dose absorbed was essentially 1 (1.1, 1.0, and 0.98 in groups A, B, and C, respectively) (Table 2). The maximum fluconazole concentrations achieved after oral dosing were similar in all three groups (Fig. 2), and the time to achievement of these peak concentrations did not differ between the groups (median [range], 1.3 h [0.5 to 7.0 h], 1.1 h [0.5 to 3.9 h], and 1.3 h [0.5 to 8.2 h] for groups A, B, and C, respectively).

Other pharmacokinetic parameters. The total plasma clearance of fluconazole (absolute clearance, calculated from the intravenous doses) was significantly lower in the group of sub-

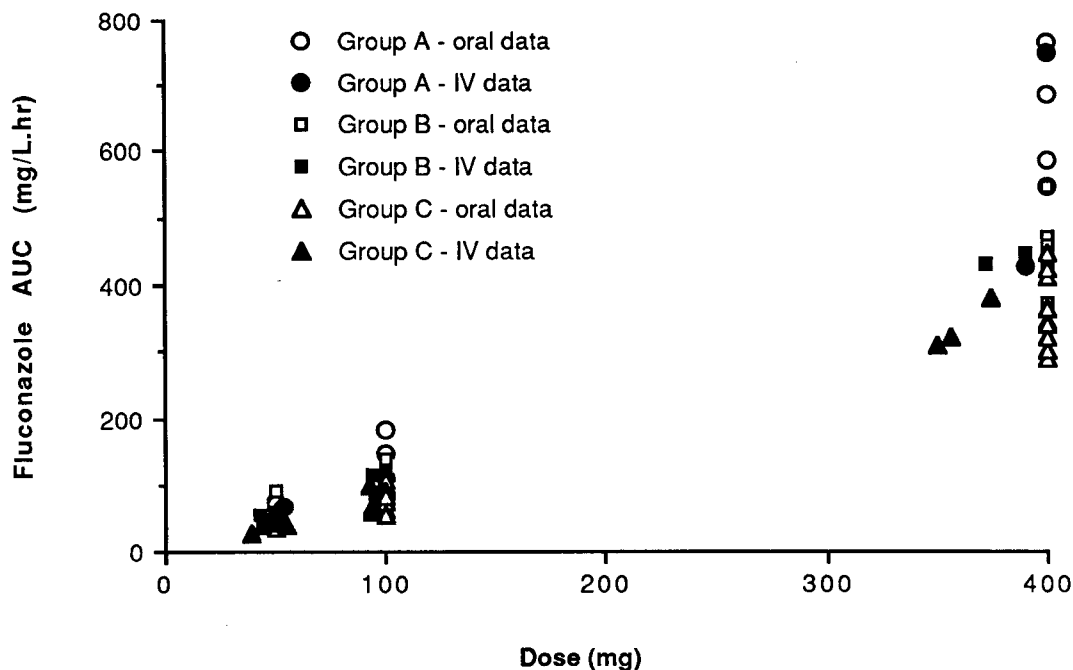


FIG. 1. AUC versus dose. Exact intravenous (IV) doses were estimated by weight, as described in Materials and Methods.

jects with CD⁺ T-cell counts of less than 200 cells per mm³ (Table 2). Figure 3 shows the fluconazole clearance in each group ($P > 0.05$ for group A versus group B; $P < 0.05$ for group A versus group C and for group B versus group C).

In the two groups of subjects with HIV infection, there was no correlation between CD4⁺ T-cell counts and estimated creatinine clearance ($r = 0.026$; $P = 0.941$) or between age and fluconazole clearance ($r = 0.124$; $P = 0.717$). For all three groups of subjects together, i.e., those with HIV infection and

the controls, there was a significant correlation between age and fluconazole clearance ($r = 0.58$; $P = 0.006$) but no correlation between fluconazole clearance and estimated creatinine clearance ($r = 0.226$; $P = 0.324$).

The volume of distribution of fluconazole was lower in the groups of subjects with HIV infection (Table 2), even when the results were corrected for weight ($P = 0.04$). The group of subjects with HIV infection and low CD4⁺ T-cell counts had the longest elimination half-life of fluconazole (Table 2; $P >$

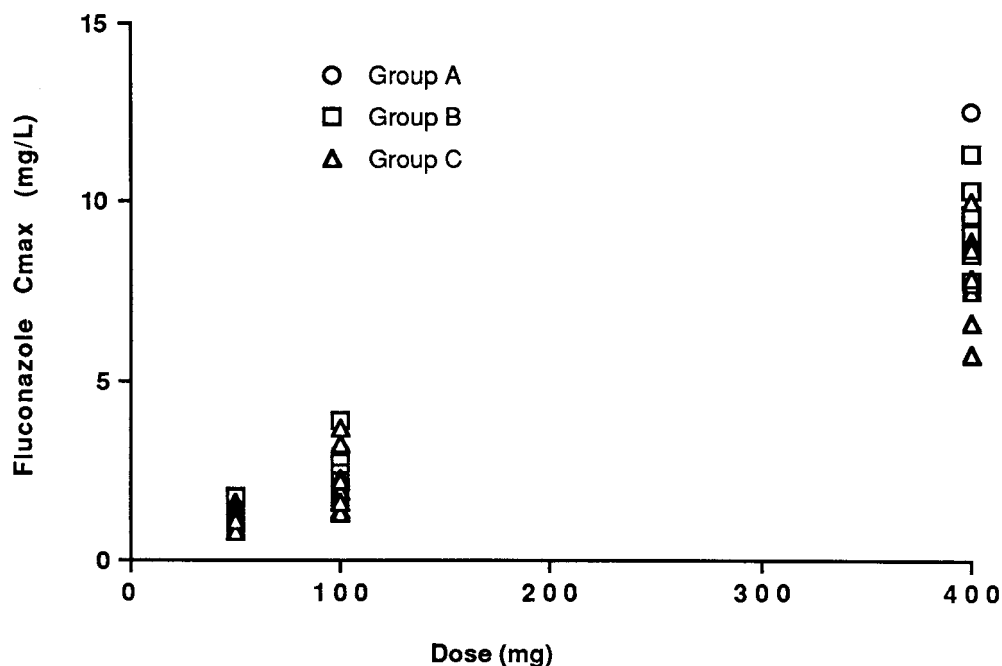


FIG. 2. Maximum fluconazole concentration after oral dosing (C_{max}) versus dose.

TABLE 2. Summary of pharmacokinetic parameters of fluconazole^a

Group ^b and subject	<i>t</i> _{1/2} (h) ^c	Size of i.v. dose (mg)	<i>F</i>	CL (liters/h)	<i>V</i> _{ss} (liters)
Group A					
A1	69	400	1.02	0.53	56
A2	32	390	1.24	0.91	45
A3	63				
A4	37	53	1.14	0.78	33
Mean (±SD)	50 (±18)*		1.13 (±0.11)†	0.74 (±0.19)**	45 (±12)††
Group B					
B1	25	95	1.29	1.19	44
B2	42	372	0.95	0.87	47
B3	36	390	1.03	0.87	42
B4	25	46	0.92	1.18	41
B5	26	44	1.19	1.19	46
B6	31	96	0.92	0.85	40
B7	29	94	1.15	0.82	31
B8	42	42	0.84	0.76	41
B9	35				
Mean (±SD)	32 (±7)*		1.04 (±0.16)†	0.97 (±0.19)**	42 (±5)††
Group C					
C1	36	94	0.87	1.38	78
C2	34	55	1.62	1.38	61
C3	33	350	1.03	1.13	49
C4	37	374	0.85	0.98	50
C5	33	49	0.86	0.89	43
C6	38	49	0.98	1.11	60
C7	46	92	0.78	0.93	58
C8	38	94	0.89	1.57	63
C9	36	39	0.97	1.34	78
C10	31	356	0.94	1.11	42
Mean (±SD)	36 (±4)*		0.98 (±0.24)†	1.18 (±0.23)**	58 (±13)††

^a Abbreviations: *t*_{1/2}, half-life; i.v., intravenous; *F*, fraction of oral dose absorbed, CL, clearance; *V*_{ss}, volume of distribution at steady state. Analysis of variance: *, *P* = 0.01; †, *P* = 0.49; **, *P* = 0.01; ††, *P* = 0.008.

^b See Table 1, footnote *b*.

^c Mean of results for oral and intravenous doses.

0.05 for group B versus group C, and *P* < 0.05 for group A versus group B and group A versus group C).

Only eight subjects collected urine (two each in groups A [subjects A1 and A2] and B [subjects B2 and B3] and four in group C [subjects C2, C3, C4, and C5]), and only two of these (C4 and C5) provided complete collections for all doses. The other urine collections were sparse, often only over the first 8 to 10 h after one or more doses. The mean renal clearance of fluconazole tended to be lower in those groups with HIV infection (0.20 [±0.08] liter/h and 0.58 [±0.02] liter/h for groups A and B, respectively; 0.79 [±0.23] liter/h for group C), although this difference was statistically significant only for the comparison between the group with the lowest CD4⁺ T-cell count and the non-HIV-infected control group (*P* = 0.10) (*P* < 0.05 for group A versus group C; *P* > 0.05 for group B versus group C and for group A versus group B).

DISCUSSION

The pharmacokinetics of fluconazole were linear in both HIV-infected subjects and controls. Not all subjects received four doses as originally planned. One subject (subject A3) withdrew because of other illnesses, one (subject B9) did not return after the first dose, and one (subject B8) elected to have two doses. The data for the completed doses are included in the analyses.

The bioavailability in all subjects, at all three doses studied, was rapid and complete. There was an unexplained error in the AUC after the 50-mg oral dose for subject C2 (Table 2). When the dose-normalized AUCs for the 100- and 400-mg oral doses were compared with the dose-normalized AUC after intravenous dosing, absolute bioavailabilities of 1.05 and 1.00, respectively, were obtained.

The null hypothesis of no difference in the pharmacokinetics of fluconazole in people with HIV at two different stages of infection and in noninfected individuals can be rejected. The lower total clearance of fluconazole in volunteers with HIV infection and a low CD4⁺ T-cell count (<200 cells per mm³) than in the other volunteers with HIV infection and in the non-HIV-infected subjects, is unlikely to be due to chance (*P* < 0.05). The volume of distribution and half-life also differed between the groups of HIV-infected and control subjects.

There were age differences between the people with HIV infection and the noninfected controls. Fluconazole clearance was inversely correlated with age for all of the subjects, although there was no such correlation for just the subjects with HIV infection. The question is whether age is a true confounder (i.e., a de facto measure of CD4⁺ T-cell count) or whether age per se causes a true difference in fluconazole clearance. A previous paper has reported no effect on half-life attributable to age in a group of subjects over 65 years of age (the mean half-life was reported to be 37 h, which is similar to

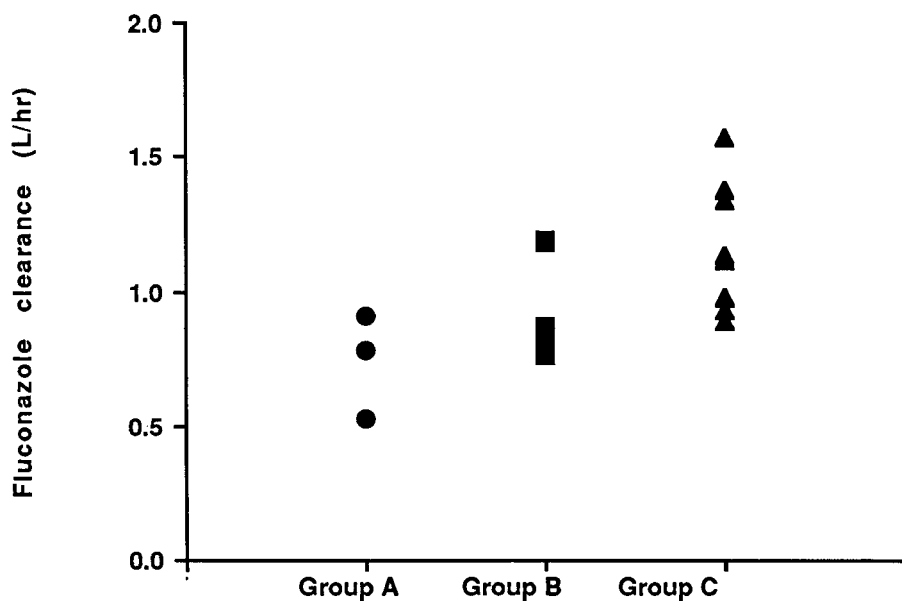


FIG. 3. Plasma clearance (absolute) of fluconazole in all subjects from groups A, B, and C.

that for the controls in the present study) (5). The mean age in group A in the present study was 37 years; the mean age in group C was 24 years. It is unlikely that this age difference alone can account for the mean 37% difference in fluconazole clearance between the groups. The mean ages in groups B and C were the same, but there was still a 20% difference in fluconazole clearance between the groups. It is unlikely that age alone was responsible for alterations in fluconazole clearance.

Another potential confounding factor is renal function. However, there was no correlation between estimated creatinine clearance and fluconazole clearance in the present study. Other investigators have reported decreased fluconazole clearance in people with impaired renal function (9); however, fluconazole clearances of as low as 0.7 liter/h (similar to that calculated in the present study for group A) have been reported only for groups with creatinine clearances of 2.4 liters/h (18). This is half of the lowest value estimated in the present study (4.8 liters/h).

In normal volunteers, renal clearance has been estimated to account for between 70 and 80% of total fluconazole clearance (9). It was unfortunate that in the present study more urine data were not available, as definite conclusions should not be drawn from the small amount of data collected. It appeared that renal clearance of fluconazole accounted for a much lower proportion of total clearance in those with HIV infection and low CD4⁺ T-cell counts (27%). There were no extra peaks on the chromatograms indicating potential metabolites. It is possible that in the HIV-infected group secretion of fluconazole is less and/or reabsorption is higher. The Cockcroft-Gault nomogram may be inaccurate as a measure of glomerular filtration rate for people with HIV infection. This is worth further investigation, since this is a common nomogram used to determine the dosage of renally eliminated drugs. Specific effects of the viral infection upon drug disposition processes do not appear to have been studied, although renal pathology has been reported (4).

One previous study found no differences in fluconazole pharmacokinetics between people with AIDS and historic controls (11). The clearance values after the intravenous dose, 0.53 to 1.49 liters/h, encompass the values determined in the

present study. The mean fraction of an oral tablet dose absorbed was 1.0, which is also in agreement with the data for the capsule reported here.

The findings of another study indicated that fluconazole clearance after a single 100-mg intravenous dose was lower in AIDS patients (CD4⁺ T-cell counts, 5 to 99/mm³) than in a concurrent control group (mean, 1.02 and 1.38 liters/h, respectively; $P < 0.05$) (22). These estimates are slightly higher than those obtained in the present study, possibly because of different methods of drug and data analysis. Also, the subjects in the previous study were on average 13% lighter than those in the present study. One case study of a patient with AIDS reported a clearance of 0.57 liter/h (6), but this patient had an estimated creatinine clearance of only 3.7 liters/h.

In the present study, subjects with HIV infection were screened carefully. None had diarrhea, were emaciated or underweight, or had abnormal liver function tests. The stringent criteria caused a problem with recruitment (19). Potential recruits for the group with lower CD4⁺ T-cell counts were especially likely to be ill, to be taking potentially interacting medications, or to have pathology excluding them from the study. However, the differences in kinetic parameters were large, so that even with the small numbers of subjects available, statistically significant differences were detected.

Subjects with HIV infection were taking a range of other medications (Table 1), but only subject B8 was taking a potentially interacting drug (ranitidine, which may affect absorption because of increased gastric pH). However, the bioavailability data for this subject were similar to those for other subjects.

Another study has demonstrated lower clearance of a drug, clindamycin, in patients with AIDS (13). Clindamycin is eliminated primarily by metabolism, with only 10% excreted unchanged; therefore, no parallels with the findings of this study can be drawn.

A study of folic acid disposition in people with HIV infection suggested that absorption of this compound was impaired (16). Another possible interpretation of those blood concentration-time data could be that clearance was altered (increased), although it is not possible to determine this from the oral data presented.

In conclusion, the main findings of this study are as follows. (i) The pharmacokinetics of fluconazole are linear over the dosing range of 50 to 400 mg for both intravenous and oral administration. (ii) The absolute bioavailability of the commercially available oral capsule of fluconazole is essentially one in people with and without HIV infection. (iii) The total plasma clearance and volume of distribution of fluconazole were lower in a group of people with HIV infection and low CD4⁺ T-cell counts than in a group with higher CD4⁺ T-cell counts and in uninfected subjects.

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REFERENCES

1. **Badewitz-Dodd, L. H. (ed.)**. 1994. MIMS annual, 18th ed. MIMS Australia, Sydney, Australia.
2. **Barone, J. A., J. G. Koh, R. H. Bierman, J. L. Colaizzi, K. A. Swanson, M. C. Gaffar, B. L. Moskovitz, W. Mechlinski, and V. Van de Velde**. 1993. Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. *Antimicrob. Agents Chemother.* **37**:778-784.
3. **Blum, R. A., D. T. D'Andrea, B. M. Florentino, J. H. Wilton, D. M. Hilligoss, M. J. Gardner, E. B. Henry, H. Goldstein, and J. J. Schentag**. 1991. Increased gastric pH and the bioavailability of fluconazole and ketoconazole. *Ann. Intern. Med.* **114**:755-757.
4. **Bourgoignie, J. J.** 1990. Renal complications of human immunodeficiency virus type 1. *Kidney Int.* **37**:1571-1584.
5. **Brammer, K. W., P. R. Farrow, and J. K. Faulkner**. 1990. Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev. Infect. Dis.* **12**:318-326.
6. **Chin, T., I. W. Fong, and A. Vandenbroucke**. 1990. Pharmacokinetics of fluconazole in serum and cerebrospinal fluid in a patient with AIDS and cryptococcal meningitis. *Pharmacotherapy* **10**:305-307.
7. **Cockcroft, D. W., and M. H. Gault**. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* **15**:31-41.
8. **Daneshmend, T. K., and D. W. Warnock**. 1988. Clinical pharmacokinetics of ketoconazole. *Clin. Pharmacokinet.* **14**:13-34.
9. **Debruyne, D., and J.-P. Ryckelynck**. 1993. Clinical pharmacokinetics of fluconazole. *Clin. Pharmacokinet.* **24**:10-27.
10. **Debruyne, D., J.-P. Ryckelynck, M.-C. Bigot, and M. Moulin**. 1988. Determination of fluconazole in biological fluids by capillary column gas chromatography with a nitrogen detector. *J. Pharm. Sci.* **77**:534-535.
11. **DeMuria, D., A. Forrest, J. Rich, J. M. Scavone, L. G. Cohen, and P. H. Kazanjian**. 1993. Pharmacokinetics and bioavailability of fluconazole in patients with AIDS. *Antimicrob. Agents Chemother.* **37**:2187-2192.
12. **Forsmark, C. E.** 1993. AIDS and the gastrointestinal tract. *Postgrad. Med.* **93**:143-148.
13. **Gatti, G., J. Flaherty, J. Bupp, J. White, M. Borin, and J. Gambertoglio**. 1993. Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. *Antimicrob. Agents Chemother.* **37**:1137-1143.
14. **Grant, S. M., and S. P. Clissold**. 1990. Fluconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* **39**:877-916.
15. **Milatovic, D., and A. Voss**. 1992. Efficacy of fluconazole in the treatment of systemic fungal infections. *Eur. J. Clin. Microbiol. Infect. Dis.* **11**:395-402.
16. **Revell, P., M. J. O'Doherty, A. Tang, and G. F. Savidge**. 1991. Folic acid absorption in patients infected with the human immunodeficiency virus. *J. Int. Med.* **230**:227-231.
17. **Sugar, A. M.** 1990. Treatment of fungal infections in patients infected with the human immunodeficiency virus. *Pharmacotherapy* **10**:154S-158S.
18. **Toon, S., C. E. Ross, R. Gokal, and M. Rowland**. 1990. An assessment of the effects of impaired renal function and haemodialysis on the pharmacokinetics of fluconazole. *Br. J. Clin. Pharmacol.* **29**:221-226.
19. **Unadkat, J. D., and J. M. Agosti**. 1990. Problems in pharmacokinetic investigations in patients with HIV infection. *Clin. Pharmacokinet.* **19**:172-176.
20. **Van Der Meer, J. W., J. J. Keuning, H. W. Scheijgrong, J. Heykants, J. Van Cutsen, and J. Brugmans**. 1980. The influence of gastric acidity on the bioavailability of ketoconazole. *J. Antimicrob. Chemother.* **6**:552-554.
21. **Yamaoka, K., T. Nakagawa, and T. Uno**. 1978. Application of Akaike's Information Criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J. Pharmacokinet. Biopharm.* **6**:165-175.
22. **Yeates, R. A., M. Ruhnke, G. Pfaff, A. Hartmann, M. Trautmann, and E. Sarnow**. 1994. The pharmacokinetics of fluconazole after a single intravenous dose in AIDS patients. *Br. J. Clin. Pharmacol.* **38**:77-79.