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Pharmacokinetics of Oral Fluconazole When Used for Prophylaxis in Bone Marrow Transplant Recipients

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The pharmacokinetics of fluconazole was investigated in 20 bone marrow transplant patients following oral administration of 200 mg of this drug. Blood samples were collected from each patient at different time intervals within 48 h after the first dose, and fluconazole was measured in plasma by high-performance liquid chromatography with UV detection. Urine was collected from 14 of these patients and analyzed similarly. The plasma concentration-time data exhibited the characteristics of the one-compartment model with first-order absorption quite well. The means ± standard deviations of half-lives for absorption and elimination, peak concentration, time to peak, mean residence time, apparent volumes of distribution, area under the curve, and apparent oral clearance observed in these patients were 2.84 ± 1.34 h, 19.94 ± 18.7 h, 4.45 ± 1.86 μg/ml, 8.34 ± 5.97 h, 39.57 ± 20.5 h, 0.874 ± 0.48 liter/kg, 156.0 ± 60.6 μg · h/ml, and 0.0256 ± 0.0138 liter/h · kg, respectively. The amount of fluconazole excreted in urine in 24 h was 67.1 ± 83 mg, which represents 33.55% ± 41.6% of the dose administered. Patients who developed hemorrhagic cystitis excreted significantly ($P \leq 0.0094$) more fluconazole in 24 h than did those who did not.

Fluconazole is a fluorine-substituted bis-triazole antimycotic agent with demonstrated activity against a host of superficial and invasive fungal infections. Bone marrow transplant (BMT) recipients are at marked risk of morbidity and mortality from these infections (15). Recent reports have indicated that fluconazole administered at prophylactic doses reduces fungal infection and colonization and enhances survival (4, 7, 21, 22). Hence, this drug is now routinely employed in these patients (4, 7, 22).

Because of favorable physicochemical properties, fluconazole is well absorbed from the gastrointestinal tract (fraction of oral dose absorbed exceeds 90%) (11, 16, 18), and its absorption appears to be independent of gastric pH (19, 25) or presence of food (13, 24). Hence, oral dosage forms (i.e., capsules, tablets, or solution) have been used as effectively as intravenous forms.

The pharmacokinetics of this drug has been well studied both in healthy subjects (5, 13, 17) and in immunocompromised patients (2, 11, 18, 23). Because of age differences in the pharmacokinetics of fluconazole, more emphasis has recently been placed on the pediatric population (1, 9, 10, 16). Thus, while two reports have been published on the pharmacokinetics of this drug in pediatric patients with hematological diseases (10, 16), there is only one published short report involving several adult BMT recipients (12).

We undertook to investigate in this report the pharmacokinetics of fluconazole in adult BMT patients following oral administration. Since some of these patients developed hemorrhagic cystitis (HC), a major urotoxicity associated with cyclophosphamide administration, the impact of HC on the pharmacokinetics of fluconazole was also examined.

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MATERIALS AND METHODS

Patients. Twenty patients with leukemia (five with acute lymphocytic leukemia [ALL], seven with chronic myelocytic leukemia [CML], and six with acute myeloid leukemia [AML]) or aplastic anemia (AA) (two patients) who underwent BMT at the King Faisal Specialist Hospital entered this study. The work was approved by the Clinical Research and Ethics Committees of the Research Advisory Council at this institution, and each patient gave informed consent in accordance with the Helsinki Declaration Accords. Admission into this study was limited to patients who were between 15 and 50 years of age and already neutropenic (neutrophils, $<0.1 \times 10^9$/liter) or at imminent risk (i.e., neutrophils, $<1.5 \times 10^9$/liter and falling because of chemotherapy) and who had no known azole hypersensitivity, no preexisting renal or hepatic dysfunction (creatinine, >115 μmol/liter; bilirubin, >21 μmol/liter; alanine aminotransferase, >45 U/liter), no preexisting or prior clinical fungal infection, no antifungal medication within the last 8 weeks, and no expected survival time from their disease of less than 3 weeks or an Eastern Cooperative Oncology Group (ECOG) score of 3 or 4.

Regular routine hematology and biochemical profiles were monitored per the usual BMT unit policy at this institution.

Drug administration. Fluconazole was administered orally to the patients in the form of a capsule (Diflucan; Pfizer Ltd., Sandwich, England) at a dose of 200 mg once daily, which was repeated for a minimum of 27 days for prophylaxis. No fluconazole was given on day 2 to permit the collection of concentration-time data over 48 h after the first dose.

The BMT conditioning regimen for patients with ALL or AML consisted of cyclophosphamide (60 mg/kg of body weight) infused over 1 h on day -5 and day -4 prior to BMT combined with 12 Gy of total body irradiation given in two daily fractions on days -2, -1, and -0 prior to BMT. For patients with CML, the regimen consisted of busulfan (1 mg/kg) given orally every 6 h on days -10, -9, -8, and -7 prior to BMT followed by cyclophosphamide (50 mg/kg) infused over 1 h on days -5, -4, -3, and -2 prior to BMT. For patients with AA, the regimen comprised cyclophosphamide (50 mg/kg) infused over 1 h on days -5, -4, -3, and -2 prior to BMT. All patients received mesna as a uroprotective agent and diphenylhydramine and metoclopramide as antiemetic drugs in addition to other medications as needed.

Specimen collection. After the first dose was administered, a blood sample (5 ml) was collected from each patient via a Hickman line lumen into a heparinized tube (Becton Dickinson Vacutainer Systems, Rutherford, N.J.) at different time intervals, i.e., at 0.33, 0.83, 2, 4, 12, 18, 24, 36, and 48 h. An additional sample was collected immediately prior to drug administration to serve as a blank. The urine excreted during the 24 h after the first dose was also collected in a 4-liter plastic container to which 2 g of sodium metabisulfite was added as an antioxidant and kept refrigerated at 4°C. At the end of the 24-h period, the urine volume was measured and an adequate aliquot (10 ml) was stored at −80°C until analysis. Blood samples were centrifuged immediately after collection at 600 × *g* for 10 min, and plasma was transferred into a new tube and stored at −80°C until analysis. For clinical reasons, urine was not collected from six of the patients included.

TABLE 1. Clinical characteristics of patients

Patient no.	Sex	Age (yr)	Wt (kg)	Ht (cm)	Creatinine clearance (ml/s)	Concn in serum		Diagnosis	HC
						ALT[a] (U/liter)	Bilirubin (μmol/liter)		
1	M	15	25.8	120	1.9	186	7	AA	−
2	F	38	58.6	135	0.4	41	35	CML	−
3	F	40	78.9	153	1.6	7	9	AML	−
4	F	44	44.5	148	1.1	30	27	CML	−
5	M	35	63.8	156	2.4	10	8	AML	−
6	M	44	68.3	167	1.9	38	9	ALL	+
7	M	35	60.0	161	1.3	47	6	ALL	−
8	F	46	71.2	154	0.8	127	6	CML	−
9	F	35	67.7	163	0.7	8	5	AML	−
10	F	35	54.5	154	1.1	11	11	AML	−
11	M	25	72.5	172	1.1	23	17	ALL	−
12	M	26	63.2	174	2.0	32	16	ALL	−
13	F	24	51.4	156	1.0	10	14	CML	−
14	F	28	39.0	149	1.1	66	19	AA	−
15	M	15	40.8	158	0.7	16	11	ALL	−
16	M	31	97.7	170	1.6	61	83	CML	−
17	M	38	72.4	165	1.3	14	37	AML	+
18	F	25	49.0	153	1.6	16	14	CML	+
19	M	20	51.5	167	1.1	25	13	ALL	−
20	M	35	68.0	167	1.6	26	18	CML	+
Mean ± SD		31.7 ± 9.2	59.9 ± 16.1	158 ± 11.8	1.32 ± 0.51	39.7 ± 44.4	18.3 ± 17.7		

[a] ALT, alanine aminotransferase.

Analysis of fluconazole in plasma and urine. Fluconazole was analyzed in patients' plasma and urine samples by high-pressure liquid chromatography with UV detection according to a slightly modified version of the method described by Inagaki et al. (8).

In summary, the drug and internal standard (miconazole) are separated on a 5-μm-particle-packed Resolve C_{18} cartridge (8 mm by 10 cm; Waters Associates, Milford, Mass.) using a mixture of 25 mM Tris buffer (adjusted to pH 7 with monobasic sodium phosphate):acetonitrile (75:25, vol/vol) as a mobile phase. C_{18} bounded SepPak cartridges (Waters Associates) were used for cleanup of the samples. The cartridge is connected to the bottom of a 10-ml Luer syringe that fits the top of the vacuum manifold cover. Each cartridge is preconditioned by consecutive washings with 4 ml of methanol followed by 4 ml of 0.1 M sodium phosphate buffer adjusted to pH 6.0 with phosphoric acid. Plasma (1 ml) is spiked with 100 μg of internal standard and diluted with 2 ml of the above-mentioned phosphate buffer. The diluted plasma is applied to the cartridge under light vacuum (9 to 10 lb/in^2), and the cartridge is washed with 4 ml of 0.1 M sodium phosphate buffer (pH 6.0). The cartridge is then dried under relatively strong vacuum (18 to 20 lb/in^2), and the drug and internal standard are eluted with 2 ml of methanol. The eluate is completely evaporated under a gentle stream of nitrogen gas, and the residue is reconstituted in 210 μl of mobile phase. A 100-μl aliquot is injected into the chromatograph. The concentration of fluconazole is calculated by using standard curves in the range 0.25 to 40 μg/ml prepared under identical conditions on the same day. Under these conditions, the peak height ratio (drug/internal standard) varied linearly ($r > 0.997$) with the concentration, and the within- and between-day coefficients of variation of the concentration at low and high concentrations (i.e., 1 and 10 μg/ml) were consistently <6.9 and <9.1%, respectively. The assay sensitivity (peak = three times the baseline noise) was 0.1 μg/ml.

Pharmacokinetic calculations. The concentration-time data obtained for each patient were subjected to a non-linear-regression analysis according to the one-compartment open model with first-order absorption phase (6) using a Model-PK personal computer package (McPherson Scientific, Rosanna, Victoria, Australia). The values of various pharmacokinetic parameters (area-under-the-curve [AUC], time-to-peak [t_{max}], peak concentration [C_{max}], apparent first-order rate constants for absorption [k_a] and elimination [k_e], and half-lives for absorption [$t_{1/2a}$] and elimination [$t_{1/2}$], mean residence time, apparent oral clearance [CL/F], and apparent volume of distribution [V/F]) were computed.

The fraction of fluconazole dose excreted in urine in 24 h (f_{u24}) was calculated according to the following equation, assuming complete absorption:

$$f_{u24} = \frac{A_{u24}}{D}$$

where A_{u24} is the amount of fluconazole excreted in urine in 24 h, and D is the dose.

Statistical analysis. The data generated were subjected to appropriate statistical analyses with the STATGRAPHICS Statistical Graphic System package (Statistical Graphics Co., Rockville, Md.) or SAS statistical package version 6.09 (SAS Institute, Cary, N.C.), and various statistical parameters were computed. A level of significance (P) in the difference or correlation was considered significant if $P \leq 0.05$.

RESULTS

Table 1 presents clinical data for the patients (11 males and 9 females) included in this study. As shown in this table, the age ranged between 15 and 46 years with a mean ± standard deviation (SD) of 31.7 ± 9.2 years. The means ± SDs of body weight and height were 59.9 ± 16.1 kg and 158 ± 11.8 cm, respectively, and the renal clearance of creatinine and concentrations of alanine aminotransferase and bilirubin in serum were 1.32 ± 0.51 ml/s, 39.7 ± 44.4 U/liter, and 18.3 ± 17.7 μmol/liter, respectively.

A plot of the mean plasma concentration-time data generated according to the one-compartment open model with first-order absorption is presented in Fig. 1. The data for each of the patients included were normalized to a 70-kg individual prior to calculating the mean and SD. As demonstrated in this model-predicted curve, the data conformed well to the one-compartment open model with first-order absorption; the observed minus predicted sum of square of residuals was small and randomly distributed around the predicted line with the correlation coefficient (r) ranging between 0.9099 and 0.9920 and the mean at 0.9534 ($n = 20$). The mean ± SD of the k_a and k_e obtained from the fit were 0.578 ± 1.38 and 0.0512 ± 0.0263 h^{-1}, respectively. Other pharmacokinetic parameters generated for the patients are presented in Table 2.

As shown in Table 2, the means ± SDs of $t_{1/2a}$ and $t_{1/2}$ of fluconazole in these patients were 2.84 ± 1.34 and 19.94 ± 18.7 h, respectively, and the C_{max} (4.45 ± 1.86 μg/ml or 1.34 ± 0.59 μg · ml^{-1}/mg · kg^{-1}) was reached at 8.34 ± 5.97 h. The model-independent parameters, AUC and CL/F, were 156.0 ± 60.6 μg · h/ml (or 47.7 ± 21.6 μg · h · ml^{-1})/mg · kg^{-1}) and 0.0256 ± 0.0138 liter/h · kg, respectively, and the V/F was 0.874 ± 0.483 liter/kg. The amount of fluconazole excreted in

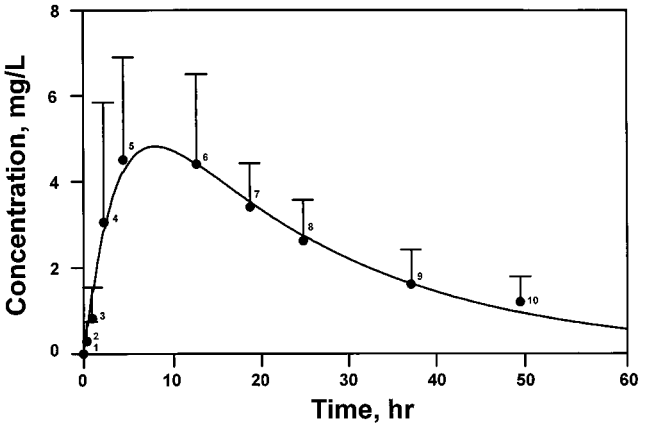

FIG. 1. Plot of the mean plasma concentration-time data generated according to a one-compartment open model with first-order absorption. The data for each patient included were normalized to a 70-kg individual prior to calculating the mean and SD. Key: ●, actual data; —, model-predicted data. Bars indicate SDs.

urine in 24 h was 67.1 ± 83.2 mg, which represents 33.55% ± 41.6% of the dose administered.

DISCUSSION

As indicated above, the pharmacokinetics of fluconazole in both volunteers and immune-compromised patients has been amply studied. However, data on the pharmacokinetics of this drug in adult BMT recipients are still lacking or inadequate at best. Indeed, the only data available on such patients are those reported by Milliken et al. (12), which were obtained from measuring fluconazole in five plasma specimens and in blanks collected from seven patients within 24 h after dosing. No pharmacokinetic analysis was performed on these data, and no pharmacokinetic parameters were reported. Because of these inadequacies, a thorough comparison between their data and ours was not feasible. The only parameters we were able to estimate from their data were f_{u24} and $t_{1/2}$. While f_{u24} was calculated by dividing the amount of fluconazole excreted in 24 h by the dose administered (D = 100 mg), $t_{1/2}$ was estimated from the ratio 0.693/−slope of the line generated from the semilogarithmic plot of fluconazole concentrations observed by these authors at 2 (peak time), 4, 8, and 24 h. The means ± SDs of f_{u24} and $t_{1/2}$ were 0.276 ± 0.086 and 20.87 ± 6.68 h, respectively. These values compare favorably with our values for these parameters (i.e., f_{u24} = 0.336 ± 0.416 and $t_{1/2}$ = 19.94 ± 18.69 h). The amount excreted in 24 h by BMT recipients was significantly reduced compared to that excreted by normal controls. Milliken et al. attributed this reduction to renal impairment in the BMT recipients caused by the conditioning regimen received by these patients (12).

It is noteworthy that among our patients from whom urine was collected (i.e., 14 patients), those who developed HC excreted within the first 24 h after dosing significantly ($P \leq$ 0.0094) more fluconazole (i.e., A_{u24} = 169.3 ± 88.4 mg, f_{u24} = 0.846 ± 0.442; n = 3) than those who did not (i.e., A_{u24} = 39.2 ± 58.8 mg, f_{u24} = 0.196 ± 0.294; n = 11). Although the cause of this increase in the renal excretion of fluconazole in patients with HC is not known, the possibilities include nephritis (3), which produces nonselective leakage or reduced tubular reabsorption of this drug brought about by the acute urotoxicity observed in these patients following cyclophosphamide administration. Also, it may be caused by a direct loss into the bladder via the inflamed hemorrhagic mucosa; however, this is

TABLE 2. Pharmacokinetic parameters of fluconazole in BMT recipients following oral administration of 200-mg capsule[a]

Patients	k_a (h^{-1})	$t_{1/2a}$ (h)	k_e (h^{-1})	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (μg/ml)	AUC (μg · h/ml)	MRT (h)	CL/F (liter/h · kg)	V/F (liter/kg)	A_{u24} (mg)	f_{u24}
All	0.578 ± 1.38	2.84 ± 1.34	0.0512 ± 0.0263	19.94 ± 18.69	8.34 ± 5.97	4.45 ± 1.86	156.0 ± 60.6	39.57 ± 20.5	0.0256 ± 0.0138	0.874 ± 0.483	67.1 ± 83.2	0.336 ± 0.416
With HC	0.278 ± 0.086	2.75 ± 1.12	0.0313 ± 0.0156	34.32 ± 32.73	11.0 ± 9.5	2.90 ± 0.43	141.2 ± 72.6	43.55 ± 23.52	0.0262 ± 0.0148	0.923 ± 0.261	169.3 ± 88.4	0.846 ± 0.442
Without HC	0.653 ± 1.55	2.86 ± 1.42	0.0562 ± 0.0066	16.34 ± 12.63	7.68 ± 4.99	4.83 ± 1.88	159.7 ± 59.3	38.57 ± 20.47	0.0255 ± 0.0141	0.862 ± 0.531	39.2 ± 58.8	0.196 ± 0.294
P[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.0094	0.0094

[a] MRT, mean residence time; NS, not significant.
[b] Level of significance of difference between patients with and without HC.

less likely (or has a smaller impact), since hematuria observed in these HC patients was not severe enough to cause this large difference (i.e., fourfold).

The pharmacokinetics of fluconazole has been described by the one-compartment (11, 18) or two-compartment (13, 16) open model with first-order absorption. Our data fitted the one-compartment model well. The use of this model was considered appropriate, since analysis of the data according to a two-compartment model yielded a similar sum of square of residuals and the rate constant for the distributive phase (α) was similar (i.e., for eight patients, almost identical) to that of the postdistributive phase (β). The values obtained in this study for AUC, C_{max}, V/F, and CL/F were in agreement with those reported by various authors (13, 14, 17, 19, 20, 23–25) for healthy volunteers following oral administration of fluconazole. However, our mean values for t_{max} (i.e., 8.3 h) and $t_{1/2a}$ (2.84 h) appear to be longer, whereas $t_{1/2}$ was shorter. This may explain the similarity between our values for AUC and those reported for healthy volunteers. Note that to our knowledge, our study is the largest to date (i.e., $n = 20$).

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