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Serum Levels of Fluconazole in Patients After Cytotoxic Chemotherapy for Hematological Malignancy

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We performed a prospective evaluation of pharmacokinetics of fluconazole administered for prophylactic purposes to 19 patients after cytotoxic chemotherapy for hematological malignancies. On days 7 and 15, we obtained 5 ml of blood from each patient. If fluconazole was administered orally, blood samples were drawn 2, 8, and 24 hr after ingestion of the drug. If it was administered intravenously, blood samples were drawn 1, 8, and 24 hr post-injection. Serum fluconazole levels were analyzed by HPLC with ultraviolet light detection. In patients receiving 200 or 400 mg of fluconazole per day, maximal serum levels were 7.9 and 15.6 mg/l and minimum levels were 5.0 and 10.3 mg/l, respectively. There was no significant difference in serum fluconazole levels comparing the levels after oral and intravenous administration, and pharmacokinetic parameters of fluconazole were comparable at each time point within one dose level. However, considerable variation in serum fluconazole levels was noted in this study, as the maximal serum levels ranged from 4.0 to 13.3 mg/l and from 8.7 to 26.9 mg/l in patients receiving 200 and 400 mg of fluconazole orally, respectively. These variations may be associated with prophylactic failures for patients with insufficient fluconazole concentrations. Multiple regression analysis showed significant correlation between serum fluconazole levels and some variables including dose of fluconazole, age, serum aspartate aminotransferase levels and blood urea nitrogen levels. These variations may be associated with disturbance of body water balance, such as massive hemorrhage and dehydration. Am. J. Hematol. 66:85–91, 2001.

Key words: fluconazole; hematological malignancy; serum level; chemotherapy

INTRODUCTION

Fungal infection is usually a fatal complication in patients undergoing cytotoxic chemotherapy for hematological malignancies, leading to high morbidity and high mortality. Early diagnosis and prompt initiation of antifungal treatment are frequently difficult in such cases, and thus prevention of fungal infection is of great importance [1]. Fluconazole and itraconazole are now widely used in chemoprophylaxis for opportunistic mycoses.

The introduction of fluconazole has had a dramatic effect on the prevention and treatment of fungal infections in patients with hematological malignancies. Widespread use of fluconazole especially reduced the incidence of candidal infection in patients undergoing bone marrow transplantation. In a prospective, randomized, placebo-controlled trial, fluconazole at a dose of 400 mg/day was shown to significantly reduce fungal colonization, superficial and hematogenous candidiasis, and mortality [2].

The pharmacokinetics of fluconazole has been well studied in healthy subjects [3,4] and HIV-positive patients [5,6]. These studies showed that fluconazole is well absorbed from the gastrointestinal tract and that its absorption, unlike that of itraconazole, appears to be independent of gastric pH or the presence of food [7]. Due

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to the little variability in the volume of body water together with some other factors, such as the high metabolic stability and the low plasma protein-binding rate of fluconazole, the blood levels of the drug show low interindividual variation in healthy subjects [8]. We have little information, however, on the pharmacokinetics of fluconazole in patients with hematological malignancies. To our knowledge, there have been only five studies involving a small number of adult leukemic patients [9–13]. Fluconazole levels were measured after administration of a single dose or several repeated doses in previous studies [4,9,10,14], and little data regarding blood levels after multiple dosing or continuous use are available. It should be noted that fluconazole is rarely prescribed in single doses. The pharmacokinetics of fluconazole may be altered after prolonged daily administration, as Nakashima et al. reported that the elimination half-life and peak time were prolonged in four patients with pulmonary cryptococcosis or aspergillosis treated orally with fluconazole for 2–6 weeks [15]. We therefore performed a prospective evaluation of the pharmacokinetics of fluconazole administered for prophylactic purposes to patients after cytotoxic chemotherapy for hematological malignancies.

PATIENTS AND METHODS

Patients

We treated 19 patients with hematological malignancies who had undergone cytotoxic chemotherapy. Written informed consent was obtained from each patient. All of the patients had received fluconazole for more than 2 weeks until enrollment, and serum fluconazole levels had already reached a plateau at the time of initiation of this study [16]. Patients were excluded from this study if they displayed evidence of an active fungal or bacterial infection or if they were receiving other systemic antifungal treatment or drugs known to interact with fluconazole such as hydrochlorothiazide, cyclosporine, cimetidine, rifampicin, tolbutamide, warfarin, or phenytoin. Renal function was estimated by calculating the creatinine clearance using the patients ideal body weight and the method of Cockcroft and Gault [17].

Fluconazole Administration

Thirteen and six patients received 200 and 400 mg of fluconazole per day, respectively. Fluconazole was administered once a day in the morning. These patients were randomly allocated to two groups (Group A and Group B). In Group A, fluconazole was administered orally from day 0 to day 7 and injected intravenously from day 8 to day 15. In Group B, fluconazole was injected intravenously from day 0 to day 7 and administered orally from day 8 to day 15. Day 0 was the day when cytotoxic chemotherapy was started. No patients vomited after fluconazole administration.

Blood Sampling

On days 7 and 15, we obtained 5 ml of blood from each patient by venipuncture. If fluconazole was administered orally, the blood samples were drawn 2, 8, and 24 hr after ingestion of the drug. If it was administered intravenously, they were drawn 1, 8, and 24 hr postinjection.

Blood samples were centrifuged immediately after they were collected, at 1,000*g* for 10 min, transferred into a new tube, and stored at −20°C until analysis.

Pharmacokinetics of Serum Fluconazole Levels

Serum fluconazole levels were measured after extraction with NaOH, ethyl acetate, and HCl, and the samples were analyzed by HPLC with ultraviolet light detection [18]. The values were normalized to a 70-kg individual prior to calculation of the mean and standard deviation. The within-assay and between-assay coefficients of variance were 11% and 12%, respectively.

The area under the serum concentration versus time curve from 0 to 24 hr (AUC 0–24) was calculated using the linear trapezoidal method.

The elimination half-life ($t_{1/2}$) was calculated as ln $2/k_{el}$, where k_{el} is the negative slope of the natural log-linear terminal portion of the serum concentration versus time curve.

Analysis of Serum Fluconazole Levels and Patients' Conditions

To investigate to which extent or in which way various conditions inherent to the patients would affect serum fluconazole levels, we examined the relation between serum fluconazole levels 1 or 2 hr after intravenous or oral administration and several parameters, namely, age, sex, chemotherapy regimens, levels of creatinine clearance, serum aspartate aminotransferase (AST) levels, serum alanine aminotransferase (ALT) levels, serum alkaline phosphatase (ALP) levels, serum lactate dehydrogenase (LDH) levels, blood urea nitrogen (BUN) levels, and sequence of oral and intravenous fluconazole administration (Group A and Group B).

Statistical Analyses

The serum fluconazole levels were analyzed using the Mann–Whitney *U*-test in cases of patients receiving 200 or 400 mg of fluconazole orally or intravenously.

We added multiple regression analysis to assess the fractionated contribution of the above-mentioned potentially predictive factors. Serum fluconazole levels showed log-normal distribution, and we used logged data in the multiple regression analysis. Factors that had a *P* value of less than 0.25 on univariate analysis were en-

TABLE I. Patients' Characteristics*

Parameters		Group A	Group B	*P* value
Dose of fluconazole	Number of patients who received 200 mg of fluconazole	7	6	
	Number of patients who received 400 mg of fluconazole	3	3	
Age		35.7 ± 12.6	43.4 ± 21.6	0.4614
Weight (kg)		53.1 ± 12.1	55.5 ± 10.3	0.9021
Height (cm)		160.7 ± 11.2	163.7 ± 7.8	0.5664
Primary malignancy	Acute lymphoblastic leukemia	3	4	
	Acute myeloblastic leukemia	3	1	
	Non-Hodgkin's lymphoma	3	3	
	Hodgkin's disease	1	0	
	Chronic myelocytic leukemia	0	1	
Cytotoxic chemotherapy	High-dose therapy	5	5	
	Conventional therapy	5	4	0.8087
Hepatic and renal function at enrollment	Serum levels of aspartate aminotransferase (IU/l)	25.9 ± 14.8	32.3 ± 16.8	0.3051
	Serum levels of alanine aminotransferase (IU/l)	45.4 ± 41.3	35.3 ± 42.5	0.3265
	Serum levels of alkaline phosphatase (IU/l)	212.6 ± 121.5	353.9 ± 386.2	0.7440
	Serum levels of cleatinine (mg/dl)	0.5 ± 0.1	0.6 ± 0.3	0.4830
	Cleatinine clearance (ml/min)	197.0 ± 120.5	154.2 ± 104.6	0.2876

*Age, weight, height, and results of the blood tests are expressed as mean ± standard deviation.

tered into the mixed-effects model. Those that contributed less than 10% to the overall ability of the model to influence serum levels of fluconazole were sequentially eliminated. The level of significance was set at $P < 0.05$.

RESULTS

Patients' Characteristics

We examined 19 patients in this study. The patients' characteristics are shown in Table I. No significant differences were observed between the two groups at the time of enrollment in this study.

The chemotherapy regimens were high-dose cytarabine and mitoxantrone (HD ara-C) ($n = 9$), EV ($n = 4$), conventional doses of cytarabine and daunorubicin ($n = 1$) [19], CHOP ($n = 2$) [20], ECAM ($n = 1$), and MICE ($n = 1$). HD ara-C consisted of 4 g/m^2 of ara-C for 4 days and 7 mg/m^2 of mitoxantrone for 2 days. EV consisted of 700 mg/m^2 of cyclophosphamide for 2 days and 700 mg/m^2 of VP-16 for 2 days. ECAM consisted of 75 mg/m^2 of VP-16 for 4 days, 75 mg/m^2 of carboplatin for 4 days, 200 mg/m^2 of ara-C for 4 days, 8 mg/m^2 of mitoxantrone for 1 day, and 20 mg/m^2 of prednisone for 14 days. MICE consisted of 500 mg/m^2 of methotrexate for 1 day, 1,000 mg/m^2 of ifosphamide for 1 day, 200 mg/m^2 of carboplatin for 4 days, and 300 mg/m^2 of VP-16 for 4 days. We defined high-dose cytarabine and MICE as high-dose regimens and the others as conventional regimens.

Two of the 13 patients receiving 200 mg of fluconazole developed deep-tissue fungal infection (*Candida tropicalis* septicemia and invasive pulmonary aspergillosis). In contrast, no fungal infection was observed among patients receiving 400 mg of fluconazole. As for other complications, a patient receiving 400 mg fluconazole (Group B) developed pseudomembranous colitis caused by *Clostridium difficile* ($n = 1$), a patient receiving 200 mg fluconazole (Group B) developed massive hemothorax associated with disseminated intravascular coagulation, and a patient receiving 200 mg fluconazole (Group B) developed massive bloody diarrhea caused by intestinal infiltration of lymphoma cells.

Pharmacokinetics of Fluconazole

The pharmacokinetics of fluconazole is shown in Table II. In cases of patients receiving either 200 or 400 mg of fluconazole, there were no significant differences in AUC0-24 between oral and intravenous administration ($P = 0.5760$ and 0.6002, respectively). However, the serum levels reached in patients receiving 400 mg of fluconazole tended to be higher than those reached in patients receiving 200 mg of fluconazole, after either oral or intravenous administration ($P = 0.0926$ and 0.0464, respectively) (Fig. 1). The elimination half-life values showed wide interpersonal variations and tended to be longer after oral than intravenous administration, but the differences were not statistically significant ($P = 0.0517$). Averages $t_{1/2}$ in each treatment group are shown in Table II.

Serum fluconazole levels showed large interindividual variation in this study. In patients receiving either oral or intravenous administration of 200 mg of fluconazole, the peak serum fluconazole levels varied from 4.0 to 13.3 mg/l. In patients receiving either oral or intravenous administration of 400 mg of fluconazole, the peak serum fluconazole levels varied from 8.7 to 26.9 mg/l.

TABLE II. Pharmacologic Parameters of Fluconazole

Dose (mg)	Route	Number of patients	C1 or 2 (mg/l)[a]	C8 (mg/dl)[b]	C24 (mg/dl)[c]	$t_{1/2}$ (hr)[d]	AUC (0–24 hr)
200	IV	13	8.0 ± 3.1	6.4 ± 2.6	4.5 ± 2.5	26.9 ± 14.2	188.8 ± 69.2
200	PO	13	7.7 ± 3.0	7.1 ± 2.9	5.4 ± 2.7	39.3 ± 22.4	186.6 ± 64.7
400	IV	6	15.9 ± 5.8	13.7 ± 5.0	10.1 ± 5.0	29.9 ± 12.9	325.1 ± 98.0
400	PO	6	15.3 ± 7.4	14.1 ± 6.9	10.4 ± 5.4	34.6 ± 8.9	342.3 ± 162.4

[a]C1, 2, 8, and 24 denote serum levels of FCZ 1, 2, 8, and 24 hr after FCZ administration, respectively.
[b]When FCZ was administered orally, its serum level 2 hr after digestion was regarded as C_{max}. When FCZ was administered intravenously, its serum level 1 hr after infusion was regarded as C_{max}.
[c]The concentration was normalized to a 70-kg individual prior to the calculation of the mean concentration.
[d]$t_{1/2}$, elimination half-life.
[e]AUC, area under the drug concentration–time curve

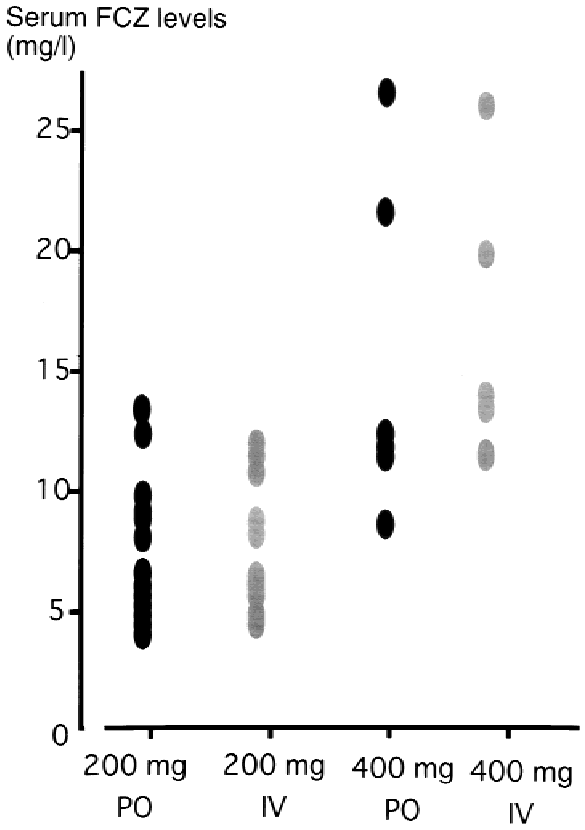

Fig. 1. Distribution of fluconazole levels. Serum levels of fluconazole in patients prescribed 400 mg of fluconazole were higher than those in patients prescribed 200 mg of fluconazole. There was considerable variation in the serum levels of fluconazole in both dosage groups.

Effect of Various Factors on Pharmacokinetic Parameters of Fluconazole

Multiple regression analysis showed a significant correlation between serum fluconazole levels 1 hr after intravenous administration and some variables including dose of fluconazole and serum AST levels (Table III) ($P = 0.021$ and 0.018, respectively). Upon intravenous administration of fluconazole, its serum levels become high in patients with low serum AST levels.

There was also a significant correlation between serum fluconazole levels 2 hr after oral administration and some variables including age and levels of BUN (Table IV) ($P = 0.026$ and 0.010, respectively). Upon oral administration of fluconazole, its serum levels become high in cases of patients with high BUN levels or with low age.

DISCUSSION

There was no significant difference in serum fluconazole levels comparing the levels after oral and intravenous administration. This indicates that the fluconazole formulation for oral administration can be well absorbed in patients with hematological malignancies as well as in healthy subjects [16]. Neither the presence of food nor gastrointestinal damage caused by chemotherapy seemed to affect the absorption of fluconazole even in patients receiving high-dose cytotoxic chemotherapies. In this respect, fluconazole is considered suitable for the treatment of hematological malignancies.

Pharmacokinetic parameters of fluconazole were comparable at each time point within one dose level. However, a considerable variation in serum fluconazole levels was noted in this study, as the serum fluconazole concentration 1 or 2 hr after administration ranged from 4.0 to 13.3 mg/l and from 8.7 to 26.9 mg/l in patients receiving 200 and 400 mg of fluconazole orally, respectively (Fig. 1). Ellis et al. [11] recently reported similar results; they noted a wide variation in peak plasma levels of fluconazole in patients undergoing cytotoxic chemotherapy for hematological malignancies. However, our findings differ from those of most previous reports that showed that there were little individual differences in serum fluconazole levels among healthy subjects [14] and leukemic patients (Table V) [9,12,13]. Considering the variability in serum levels of fluconazole after multiple doses [16] and the report that fluconazole accumulation was found to be independent of the dose in healthy subjects [18], it seems reasonable that the peak levels of fluconazole also varied greatly in our study.

These variations in the peak levels of fluconazole may not be a problem for the majority of patients taking flu-

TABLE III. Effects of Various Clinical Variables on Peak Fluconazole Levels After Intravenous Administration*

Variables	Stepwise history	Parameter estimate	*R* square	*P* value
Fluconazole dose (mg)	Locked[a]	0.002246	0.29	0.021[b]
Age	Included	−0.0061059	0.72	0.252
BUN (mg/dl)	Included	0.06628	0.5104	0.052
LDH (IU/l)	Included	0.001154	0.63	0.124
AST (IU/l)	Included	−0.01699	0.58	0.018[b]
Creatinin clearance (ml/min)	Not included	−0.00099	0.681	0.147
Body surface area (m^2)	Not included			0.678
Chemotherapy (high/ conventional)	Not included			0.891
Alkaline phosphatase (IU/l)	Not included			0.971
	Not included			0.841
ALT (IU/l)	Not included			0.677
Intercept		1.7605		

*Analysis was done with multiple stepwise regression model as described by Ln(peak fluconazole concentration) = $b_1 x_1 + b_2 x_2 + \ldots + b_1 x_1$ + Intercept. Abbreviations: BUN, blood urea nitrogen; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; and ALP, alkaline phosphatase

[a]This variable was locked to be included into the model as a regressor.

[b]Statistically significant.

TABLE IV. Effects of Various Clinical Variables on Peak Fluconazole Levels After Oral Administration*

Variables	Stepwise history	Parameter estimate	*R* square	*P* value
Fluconazole dose (mg)	Locked[a]	0.001439	0.32	0.122
Age	Included	−0.01159	0.60	0.026[b]
BUN (mg/dl)	Included	0.05786	0.44	0.010[b]
LDH (IU/l)	Not included			0.990
AST (IU/l)	Not included			0.276
Creatinin clearance (ml/min)	Not included			0.545
Body surface area (m^2)	Not included			0.752
Chemotherapy (high/ conventioinal)	Not included			0.304
Alkaline phosphatase (IU/l)	Not included			0.901
ALP (IU/l)	Not included			0.898
ALT (IU/l)	Not included			0.745
Intercept		1.800		

*Analysis was done with multiple stepwise regression model as described by Ln(peak fluconazole concentration) = $b_1 x_1 + b_2 x_2 + \ldots + b_1 x_1$ + Intercept. Abbreviations: BUN, blood urea nitrogen; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; and ALP, alkaline phosphatase.

[a]This variable was locked to be included into the model as a regressor.

[b]Statistically significant.

conazole as a prophylactic agent, but we should recognize the importance of interindividual variations. They may be critical for some patients and may be associated with the subsequent development of some types of fungal infections. The risk of candidal infection will increase in the case of patients who have low serum levels of fluconazole. In this study, the lowest serum levels of fluconazole were 1.3 and 5.2 mg/dl in the case of patients receiving 200 and 400 mg of fluconazole, respectively. In fact, a patient receiving 200 mg of fluconazole developed *C. tropicalis* septicemia in this study, and the lowest serum level of fluconazole observed was 4.6 mg/l. She did not develop significant complications except for mild diarrhea. However, this patient received intensive cytotoxic chemotherapy including corticosteroid for the treatment of refractory non-Hodgkin's lymphoma, and neutropenia less than 500/l persisted more than 2 weeks. Thus, it remains unknown whether candidemia could have been prevented if the patient had received 400 mg of fluconazole. However, invasive fungal infection did not occur among the patients receiving 400 mg of fluconazole. It is to be noted that the serum concentrations in the case of patients receiving 400 mg of fluconazole were above the minimal inhibitory concentration for most *Candida* species. Because fluconazole is tolerated well and there are few problems encountered at the higher end of the dosage range, it may be appropriate to administer 400 mg of fluconazole as anti-fungal prophylaxis rather than 200 mg.

It would be important to identify the factors influencing the pharmacokinetics of fluconazole in the treatment of hematological malignancies, but we have obtained no information on them. In this study, we found a significant association between serum fluconazole levels and three parameters, BUN levels, serum AST levels, and age, in addition to fluconazole doses. Firstly, we showed that serum fluconazole levels were elevated in patients with high BUN levels. Because fluconazole is eliminated by the kidney [16], it may be accumulated in cases of renal dysfunction. However, it should be noted that no significant association was found between serum fluconazole levels and creatinine clearance, a more sensitive marker of renal function than BUN levels, and that BUN levels are influenced by factors other than renal function, including nutritional states and body water balance. BUN levels might have reflected the latter conditions. It is reasonable that serum fluconazole levels are elevated when patients are dehydrated. Secondly, it seems quite interesting that serum fluconazole levels were inversely related to serum AST levels, although hepatic function has little influence on the pharmacokinetics of fluconazole [16] and the exact mechanism responsible for this association remains unknown. However, it is to be noted that serum AST levels were elevated in eight patients, of which three developed significant complications other than fungal infection, i.e., massive hemothorax associated with disseminated intravascular coagulation, massive diarrhea caused by intestinal infiltration of lymphoma cells and pseudomembranous colitis caused by *C.*

TABLE V. Previous Studies on the Pharmacokinetics of Fluconazole in Adult Patients With Hematological Malignanices*

Authors	Year	Chemotherapy	Number	Age (y.o.)	Duration of fluconazole administration (days)	Dose (mg)	Route	Standardization	Samples	C_{max} (mg/l)	Reference no.
Milliken et al.	1989	ABMT	7	31.1 ± 10.0	8.1 ± 3.8	100	p.o.	ND	Serum	1.8 ± 0.2	9
Lazo et al.	1994	Chemotherapy	4	31.5 ± 13.0	Single dose	100	p.o.	70 kg	Plasma	1.8 ± 0.2	10
Ellis et al.	1997	Chemotherapy	22	ND	Continuous use	200	p.o.	ND	Plasma	9.3 ± 3.7	11
El-Yazigi et al.	1997	BMT	20	31.7 ± 9.2	27	200	p.o.	70 kg	Plasma	4.5 ± 1.9	12
El-Yazigi et al.	1997	BMT	11	32.9	27	200	p.o.	ND	Plasma	10.1 ± 1.9	13
Kami et al.	2000	Chemotherapy	13	41.4 ± 19.3	>14	200	p.o	70 kg	Serum	7.7 ± 3.0	
						200	i.v.	70 kg	Serum	8.0 ± 2.9	
		Chemotherapy	6	35.0 ± 12.3	>14	400	p.o.	70 kg	Serum	15.3 ± 7.4	
						400	i.v.	70 kg	Serum	15.9 ± 5.8	

*Abbreviations: ND, not described; ABMT, autologous bone marrow transplantation; and BMT, bone marrow transplantation.

difficile. These three patients lost massive amounts of body water, and fluconazole moieties might have been excreted with it. Thus, serum fluconazole levels might have been low in these patients. This hypothesis is compatible with the recent report by El-Yazigi et al. [13], in which they showed an increased excretion of fluconazole in patients with hemorrhagic cystitis with a trend toward lower serum fluconazole concentrations. In patients who develop massive bleeding or diarrhea, the pharmacokinetics of fluconazole may be altered. Lastly, our study showed that serum fluconazole levels were inversely related to patients' age, especially in the setting of oral administration. While the exact mechanism remains unknown, fluconazole absorption may be reduced in the case of old patients, or significant complication causing loss of body water may frequently develop in these patients.

In conclusion, we showed that the fluconazole formulation for oral use was well absorbed in patients with hematological malignancies, the same as in healthy subjects, and that the pharmacokinetic parameters of fluconazole are comparable at each time point within one dose level. However, there were considerable variations in serum levels of fluconazole in patients after cytotoxic chemotherapies for hematological malignancies. Disturbance of body water balance, such as massive hemorrhage and dehydration, may be associated with these variations. Although we cannot determine the impact of the variable fluconazole levels on its prophylactic efficacy from the results of this small prospective study, the interindividual variations in fluconazole levels may be responsible for prophylactic failure in some patients with low fluconazole concentration. However, we must make some comments on the limitation of this study. The most important was the small size of this study, which limited the power of statistical testing for detecting group differences. Furthermore, few data points have been collected, and we could not clarify full pharmacokinetics of fluconazole in this study. These findings impair the validity of our conclusion. Full pharmacokinetics of fluconazole should be clarified in the further studies involving a large number of patients with hematological malignancy.

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