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SHORT REPORT

PLASMA CONCENTRATION OF ITRACONAZOLE IN PATIENTS RECEIVING CHEMOTHERAPY FOR HEMATOLOGICAL MALIGNANCIES: THE EFFECT OF FAMOTIDINE ON THE ABSORPTION OF ITRACONAZOLE

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SUMMARY

Fungal infection is a serious complication in immunocompromised patients, especially those with neutropenia. Itraconazole (ITZ) is expected to be an effective prophylactic agent for fungal infection because it has more activity against *Aspergillus* species than fluconazole and it is less toxic than amphotericin-B. However, ITZ is available only as an oral capsule, the absorption of which is thought to depend on the presence of acid in the stomach. In this study, the effect of famotidine, an H_2-blocker, on the absorption of ITZ was investigated. Patients undergoing chemotherapy for hematological malignancies were enrolled. To minimize the effect of famotidine, the time of ITZ intake was different from that of famotidine intake. The plasma concentrations of ITZ with or without taking famotidine were determined just before and 4 h after ITZ intake. Mean trough and peak concentrations of ITZ without famotidine were 332 ng/ml and 476 ng/ml, respectively. When famotidine was co-administered, the concentrations decreased to 204 ng/ml and 315 ng/ml, respectively. Statistical analyses revealed significant differences between trough concentrations in the presence and absence of famotidine ($p=0{\cdot}008$). There was also a clear tendency toward higher peak concentrations in the plasma concentrations with famotidine ($p=0{\cdot}06$). These findings suggest that famotidine decreases the plasma concentration of ITZ in patients undergoing chemotherapy. Close monitoring of the plasma concentration of ITZ and dose adjustment are required for efficient prophylaxis.

KEY WORDS famotidine; fungal infection; H_2-blocker; itraconazole; plasma concentration

INTRODUCTION

Fungal infection is a frequent complication in patients with hematological malignancies, especially in those with neutropenia. Once a fungal infection has developed, it is difficult to treat. Thus, prophylactic treatments are important for neutropenic patients. Gut decontamination is one of the prophylactic strategies, based on the fact that some fungal infections are thought to be derived from colonization in the gut.[1] Airway decontamination is also important because *Aspergillus* species, which cause fatal pneumonia, usually invade from the airways.[2] However,

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delivery of amphotericin-B (AMPH-B) directly to the sinopulmonary mucosa using a nasal spray has been reported as not reducing aspergillus infection.[3] Although reverse isolation in a laminar air flow room is the most effective method for reducing aspergillus infection,[4] that facility is not always available. Itraconazole (ITZ) is expected to be an effective prophylactic agent for fungal infections; it has more activity against *Aspergillus* species than fluconazole and is less toxic than AMPH-B.[2] In addition, the tissue distribution of ITZ is sufficient.[5] However, ITZ is available only as an oral capsule, the absorption of which is thought to depend on the presence of acid in the stomach.[5] Whether the absorption of ITZ is reduced by H_2-blockers is controversial, as conflicting results have been reported.[6,7] This point is important for patients undergoing chemotherapy, as they often need H_2-blockers to prevent the peptic ulcers caused by antineoplastic agents, glucocorticoids and mental stress.

In the present study, we investigated the effect of famotidine, a major H_2-blocker, on the absorption of ITZ to determine whether ITZ could be used as a prophylactic agent for fungal infection in patients taking H_2-blockers.

PATIENTS AND METHODS

Patients receiving chemotherapy for hematological malignancies were eligible for the study. Patients taking drugs that might interact with the absorption of ITZ, such as rifampicin or phenytoin, were excluded.[8,9] Patients who had an abnormality in either hepatic or renal function were also excluded. Written, informed consent was obtained from all patients enrolled in the study.

The administration of 40 mg/day of famotidine and 200 mg/day of ITZ was started on the first day of the chemotherapy regimen. Famotidine was given in two divided doses at 06.00 h and 21.00 h. ITZ was given in a single dose after lunch to minimize the effect of famotidine. Blood samples were taken just before and 4 h after ITZ intake on the 10th day because it takes about 7 days for the plasma concentration of ITZ to stabilize.[5] Famotidine was withdrawn on the 11th day. On the 14th day, when it was considered that the effect of famotidine would be diminished, blood samples were again taken.

The plasma concentration of ITZ was determined by high-performance liquid chromatography. The concentrations of the samples obtained just before and at 4 h after ITZ intake were considered as the trough and peak concentrations, respectively.[5]

To rule out the effect of antineoplastic agents on the absorption of ITZ, the regimen-related toxicity (RRT) of the gastrointestinal tract, including the state of appetite, was evaluated according to the guidelines of the World Health Organization.[10]

The Wilcoxon signed rank test was used for statistical analyses. A p value of less than 0·05 was considered to be significant.

RESULTS

Eighteen patients were enrolled in the study and their clinical data are shown in Table 1. Two patients (UPN10 and UPN16) were excluded from the analysis because of greater than grade II gastrointestinal RRT with severe anorexia. In the other patients, significant gastrointestinal RRT was not observed and ITZ was well tolerated.

The plasma concentration of ITZ in each of the 16 patients is shown in Table 2. The mean trough and peak concentrations of ITZ without famotidine were 332 ng/ml and 476 ng/ml, respectively. When famotidine was co-administered, these values decreased to 204 ng/ml and

Table 1. Patients' clinical data

Patient no.	Disease	Chemotherapy
UPN1	NHL in NR	CPA, ADR, VCR, PSL
UPN2	NHL in NR	CA, MIT
UPN3	ALL in CR	CA, MIT
UPN4	ALL in NR	MTX, IFM, CBDCA, ETP
UPN5	ALL in NR	CA, MIT
UPN6	NHL in NR	ETP, CBDCA, CA, MIT
UPN7	ANLL in CR	CA, MIT
UPN8	ANLL in CR	CA, MIT
UPN9	ATL in NR	CPA, ADR, VCR, PSL
UPN10	NHL in NR	ETP, CBDCA, CA, MIT
UPN11	ALL in CR	CA, MIT
UPN12	ANLL in CR	DNR, ETP, MIT
UPN13	CML in BC	ADR, VCR, CPA, MTX, PSL
UPN14	ALL in CR	CA, MIT
UPN15	MM in NR	MEL, PSL
UPN16	ANLL in NR	IDR, CBDCA, ETP

NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphocytic leukemia; ATL, adult T-cell leukemia/lymphoma; CML, chronic myelogenous leukemia; MM, multiple myeloma; CR, complete remission; NR, not in remission; BC, blastic crisis; CPA, cyclophosphamide; ADR, doxorubicin; VCR, vincristine; PSL, prednisolone; CA, cytarabine; MIT, mitoxantrone; MTX, methotrexate; IFM, ifosfamide; CBDCA, carboplatin; ETP, etoposide; DNR, daunorubicin; MEL, melphalan; IDR, idarubicin.

332 ng/ml, respectively. Statistical analysis revealed significant differences in the trough concentrations between those in the presence and those in the absence of famotidine ($p=0{\cdot}008$). There was also a clear tendency toward higher peak concentrations in those receiving famotidine ($p=0{\cdot}06$). However, the underlying disease, disease status, and the chemotherapy regimens did not affect the plasma concentrations. In the patients who had gastrointestinal RRT with severe anorexia, the concentrations of ITZ were extremely low because ITZ was taken while fasting.[11]

One patient (UPN10) had a newly developed, and one patient (UPN4) had a recurrent, pulmonary aspergillus infection diagnosed by a computed tomography scan of the chest and by the detection of aspergillus antigen. None of the other patients suffered from fungal infection.

DISCUSSION

ITZ is a new triazole that has demonstrated broad spectrum antifungal activity, including *Aspergillus* species. It has extensive tissue distribution[5] and does not have the severe toxicities, such as nephrotoxicity or anaphylaxis, frequently seen with AMPH-B. The major weakness of ITZ is its instability of absorption. We found two reports evaluating the effect of H_2-blockers on the absorption of ITZ;[6,7] however, in those studies ITZ concentrations were measured after a single administration. Thus, their data did not reflect ITZ concentrations in the steady state. In addition, their subjects were healthy volunteers. To our knowledge, the present study is the first to evaluate the effect of famotidine on the steady-state concentration of ITZ in patients undergoing chemotherapy. Our results showed that the absorption of ITZ was reduced by famotidine, even if the time of ITZ administration was shifted from that of famotidine in order to minimize their interaction.

Table 2. Plasma concentration of itraconazole

	Plasma concentration of itraconazole (ng/ml)			
	Famotidine (+)		Famotidine (−)	
Patient no.	Trough	Peak	Trough	Peak
UPN1	112	142	196	356
UPN2	268	368	336	563
UPN3	62	282	80	106
UPN4	268	358	339	380
UPN5	388	962	449	723
UPN6	180	180	878	906
UPN7	162	219	405	389
UPN8	476	565	793	966
UPN9	314	345	348	540
UPN10	ND	ND	355	531
UPN11	146	458	115	225
UPN12	206	275	305	603
UPN13	134	60	52	414
UPN14	34	36	107	112
UPN15	108	159	250	382
UPN16	11	40	18	14
Average+SD	204+126	315+238	332+247	476+262

ND, not detected; SD, standard deviation.
UPN10 and UPN16 were excluded from the analysis.

The required plasma concentration for effective prevention of fungal infections has not been determined definitely. However, Tricot *et al.*[12] reported that in neutropenic patients with a peak plasma concentration of ITZ of more than 250 ng/ml, the number of fungal infections was significantly lower than in those with a concentration of less than 250 ng/ml. From their result it seems that a peak plasma concentration of 250 ng/ml is necessary to protect neutropenic patients from fungal infections. In the present study, the peak concentrations in eight of the 16 patients taking an H_2-blocker, and in four of the 16 patients who were not taking an H_2-blocker, did not reach 250 ng/ml.

In the present study, despite the lack of a laminar air flow room, only one patient newly developed a fungal infection, and that patient's ITZ concentrations were extremely low because ITZ was taken while fasting. Although this result compares favourably with a previous group of patients whom we treated with oral AMPH-B syrup (unpublished data), a large scale prospective study is required to evaluate the effectiveness of ITZ prophylaxis.

In conclusion, ITZ seems to be a promising agent in the prevention of fungal infections. However, rapid measurement of plasma concentration and then dose adjustment are required for effective prophylaxis, especially in patients taking H_2-blockers. In addition, ITZ should be substituted with an alternative prophylactic agent in patients with severe anorexia.

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