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Pharmacokinetics of Antifungal Agent Micafungin in Critically Ill Patients Receiving Continuous Hemodialysis Filtration

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Currently in Japan, the preferred method for blood purification in patients with acute renal failure is continuous hemodiafiltration (CHDF). However, CHDF filters out various antifungal drugs such as fluconazole through large pores in the membrane used. Systemic fungal infection is still one of the main causes of death and complications in critically ill patients in intensive care units (ICUs). Therefore it is important to determine the appropriate use of antifungal agents. This study was designed to evaluate the influence of CHDF on the pharmacokinetics of the antifungal agent micafungin in ICU patients. The pharmacokinetics of micafungin were studied in four ICU patients receiving CHDF and in nine ICU patients not receiving CHDF. To evaluate the pharmacokinetics, the ratio of serum micafungin concentration to dose per body weight (C/D) was used in this study. There was no progressive accumulation or exclusion of micafungin in patients receiving CHDF. The mean (±S.D.) extraction rate (%) for micafungin during CHDF was 3.6 ±3.9. There was no significant difference in the serum micafungin C/D-time profiles between the patients receiving and not receiving CHDF. These results show that CHDF does not affect the pharmacokinetics of micafungin. Therefore it is not necessary to adjust the micafungin dose in patients receiving CHDF.

Key words——continuous hemodiafiltration; micafungin; critical care; pharmacokinetics

INTRODUCTION

Acute renal failure is a common complication in critically ill patients. Currently in Japan, the preferred method for blood purification in patients with acute renal failure is continuous hemodiafiltration (CHDF) because it enables better control of fluid balance and better metabolic control and increased hemodynamic stability and allows full nutritional support and a shorter duration of episodes of renal failure and intensive care unit (ICU) admission.[1,2] However, CHDF filters out various antimicrobial drugs such as the antifungal agent fluconazole through large pores in the membrane used. It was reported that CHDF removes fluconazole from the blood efficiently and at a high rate, resulting in an ineffective serum fluconazole level.[3] Systemic fungal infections in ICU patients are not frequent. However, their incidence is increasing in concert with high mortality and morbidity leading to prolonged stays in ICU wards.[4,5] Therefore it is important to determine the appropriate use of antifungal agents for systemic antifungal therapy.

Since 2002, the antifungal agent micafungin has often been used for systemic antifungal chemotherapy, particularly in ICUs, because of its good efficacy and the absence of serious adverse effects. However, no report has focused on the pharmacokinetics of micafungin in critically ill patients receiving CHDF. This study was designed to evaluate the influence of CHDF on the pharmacokinetics of micafungin in emergency and critical situations.

MATERIALS AND METHODS

Patients and Administration of Micafungin

This clinical study was carried out in the ICU of the Department of Emergency and Critical Care Medicine in Nippon Medical School Hospital Japan. The study protocol was approved by the institutional review board, and informed consent for participation

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was obtained from each patient or patient's family. Thirteen patients received an intravenous infusion of micafungin for systemic antifungal therapy, four of whom underwent CHDF to maintain their fluid and electrolyte balance. The daily dose administered was determined by the clinician responsible for each patient and was not influenced by the investigators.

CHDF Vascular access for CHDF was obtained by the insertion of an 11-Fr double lumen catheter (Argyle, 6011A20-W) in either the femoral or right internal jugular vein. CHDF was performed using a hollow-fiber membrane (HEMOFEEL® CH-1.0L, Toray Medical, Inc.) composed of polymethyl methacrylate membrane. Replacement fluid (Sublood BS®, Fuso, Japan) was delivered after the membrane into the venous limb of the circuit at a rate appropriate for each patient's requirements. Blood was pumped through the membrane at a rate between 1.0 and 1.5 ml/kg/min. Standard dialysate was delivered countercurrently to the blood flow at a rate of between 500 and 1000 ml/h using a volumetric pump. Ultradiafiltrate flow was set at a rate of between 800 and 1300 ml/h. Nafamostat mesilate was administered as an anticoagulant, and activated coagulation time was maintained between 150 and 180 s throughout the procedure.

Sampling and Drug Analysis Blood samples were obtained through an arterial cannula or the sampling ports of the CHDF circuit before and after filtering, and urine samples and ultradiafiltrate samples were also collected for a steady-state assay of micafungin. Serum was separated and stored at -20℃ until analyzed. The concentration of micafungin in serum was determined by high-performance liquid chromatography (HPLC). The HPLC equipment consisted of the following: an LC-10AD constant-flow pump (Shimadzu), an SIL-10Axl auto sample injector (Shimadzu), a TSK-GEL ODS-80TM column (150 mm×4.6 mm; Tosoh), and an RF-$10A_{XL}$ fluorescence detector (Ex; 273 nm, Em; 464 nm; Shimadzu). The mobile phase was acetonitrile: 0.02 mM potassium dihydrogen phosphate (41: 59 v/v) with a flow rate of 1 ml/min. FR195743, the internal standard, was prepared by dissolution in the mobile phase. The samples were extracted and test solutions were injected onto the HPLC. Linear regression analysis, which was carried out by plotting the ratios of the peak height of micafungin to that of the internal standard against the added concentrations, was used to determine the slope and intercept. Micafungin and FR195743 were provided by Fujisawa (Tokyo, Japan). Other chemicals used were of analytical or reagent grade.

Pharmacokinetic Analysis Extraction rate (ER) was calculated using the following equation[6]: ER (%) $= (C_{bi} - C_{bo}) \times 100/C_{bi}$ where C_{bi} represents the serum concentration of micafungin in the blood going in and C_{bo} represents the serum concentration of micafungin in the blood flowing out. CHDF clearance (CL_{CHDF}) was calculated from the following equation[7]: $CL_{CHDF} = Q_{bo} \times (1 - Hct) \times (C_{bi} - C_{bo})/C_{bi}$ where Q_{bo} is the blood flow rate out, Hct is hematocrit level, C_{bi} is the serum concentration of micafungin in the blood going in, and C_{bo} is the serum concentration of micafungin in the blood flowing out.

To evaluate the pharmacokinetics, the ratio of serum micafungin concentration to dose per body weight (C/D) was used in this study. A one-compartment model was used. The model was parameterized in terms of the volume of distribution (Vdss) and total clearance (CL). The serum micafungin concentrations were fitted to the pharmacokinetic model using the WinNonlin pharmacokinetic software package (Pharsight Corporation, USA). We simulated the C/D-time curves by estimating micafungin concentrations using the pharmacokinetic parameters and dividing them by dose per body weight, except that the C/D of patient 3 was excluded because of differences in administration (once a day vs twice a day).

Statistical Analysis Data are presented as mean ±standard deviation (S.D.). Student's *t*-test was used for statistical analysis, and significance was set at $p < 0.05$.

RESULTS

Clinical features of the patients and the daily doses of micafungin administered are shown in Table 1. Micafungin was administered at a dosage in the range of 150–300 mg/day to patients receiving and not receiving CHDF. The concentrations of micafungin at each sampling port of the CHDF circuit in patients 1, 2, and 3 are shown in Fig. 1. The mean (± standard deviation) micafungin concentrations in three patients at the inlet and outlet of the CHDF circuit and in the ultradiafiltrate and urine were 12.7±10.2 μg/ml, 12.3±10.1 μg/ml, not detected, and 0.2±0.1 μg/ml, respectively. There was no elimination of

Table 1. Demographic Data

Patient	Sex	Age (years)	Daily dose (mg)	BW (kg)	Primary diagnosis
1	M	83	150×1	50	Pneumonia, septic shock
2	M	84	150×1	50	Perforation of duodenal ulcer
3	M	72	150×2	78	Acute pancreatitis
4	M	72	150×1	80	Perforation of duodenal ulcer
5	M	65	150×1	56	Cerebral infarction, pneumonia
6	M	81	150×1	60	Acute pancreatitis
7	F	50	150×1	90	Perforation of rectal cancer
8	M	66	300×1	80	Renal abscess
9	M	60	150×1	90	Liver abscess
10	F	36	300×1	39	Pneumonia, anorexia nervosa
11	F	70	150×1	60	Diffuse peritonitis
12	F	66	150×1	40	Colon perforation
13	M	69	200×1	70	Rupture of abdominal aortic aneurysm
Mean		67.2	188.5	64.8	
SD		13.3	65.0	17.7	

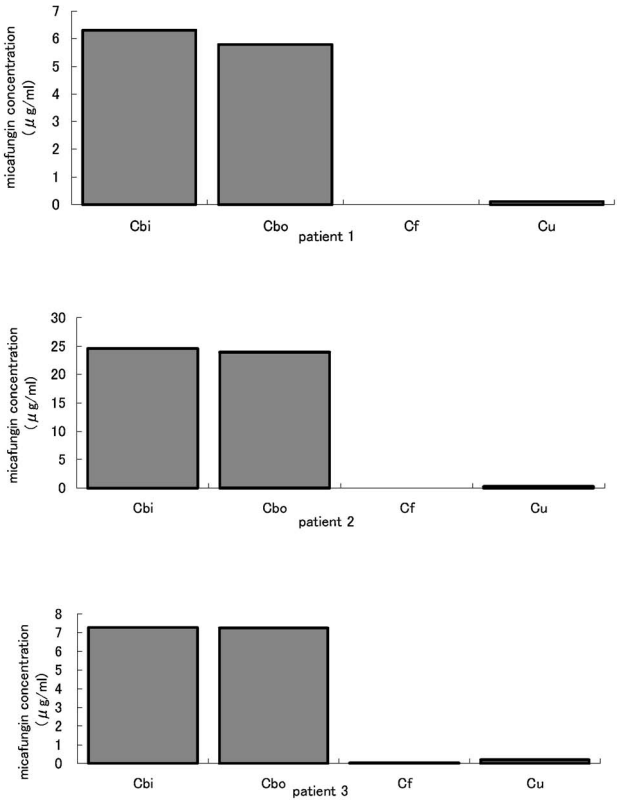

Fig. 1. Serum Micafungin Concentrations at Each Sampling Port of Continuous Hemodiafiltration

C_{bi}: concentration of blood going in, C_{bo}: concentration of blood flowing out, Cf: concentration of ultradiafiltrate, Cu: concentration of urine.

Table 2. Pharmacokinetic Parameters of Micafungin in Patients Receiving and not Receiving CHDF

Pharmacokinetic parameter	Patients receiving CHDF (mean±S.D.)	Patients not receiving CHDF (mean±S.D.)	p value
Vdss (L)	17.5±4.4	16.2±6.8	0.7361
CL (L/hr)	1.4±0.7	1.4±0.7	0.9043

CHDF: continuous hemodiafiltration, Vdss: volume of distribution at steady state, CL: clearance.

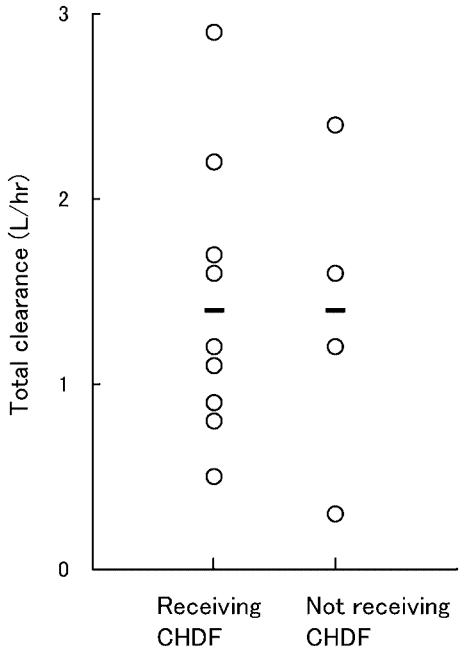

Fig. 2. Total Clearance of Micafungin in Patients Receiving and not Receiving Continuous Hemodiafiltration

Data points represent the total clearance of micafungin in patients receiving (patients 1–4) and not receiving (patients 5–13) continuous hemodiafiltration. Bars represent the mean values.

micafungin in the ultradiafiltrate. The mean (± standard deviation) ER (%) for micafungin was 3.6±3.9. The mean (± standard deviation) CL_{CHDF} (ml/min) was 1.7±1.5.

The values of pharmacokinetic parameters in the patients receiving (patients 1–4) and not receiving (patients 5–13) CHDF are shown in Table 2 and Fig. 2. No significant differences in the pharmacokinetic parameters were observed between the two groups. The mean serum micafungin C/D-time profiles after once-a-day administration to patients receiving (patients 1, 2, and 4) and not receiving (patients 5–13) CHDF are shown in Fig. 3.

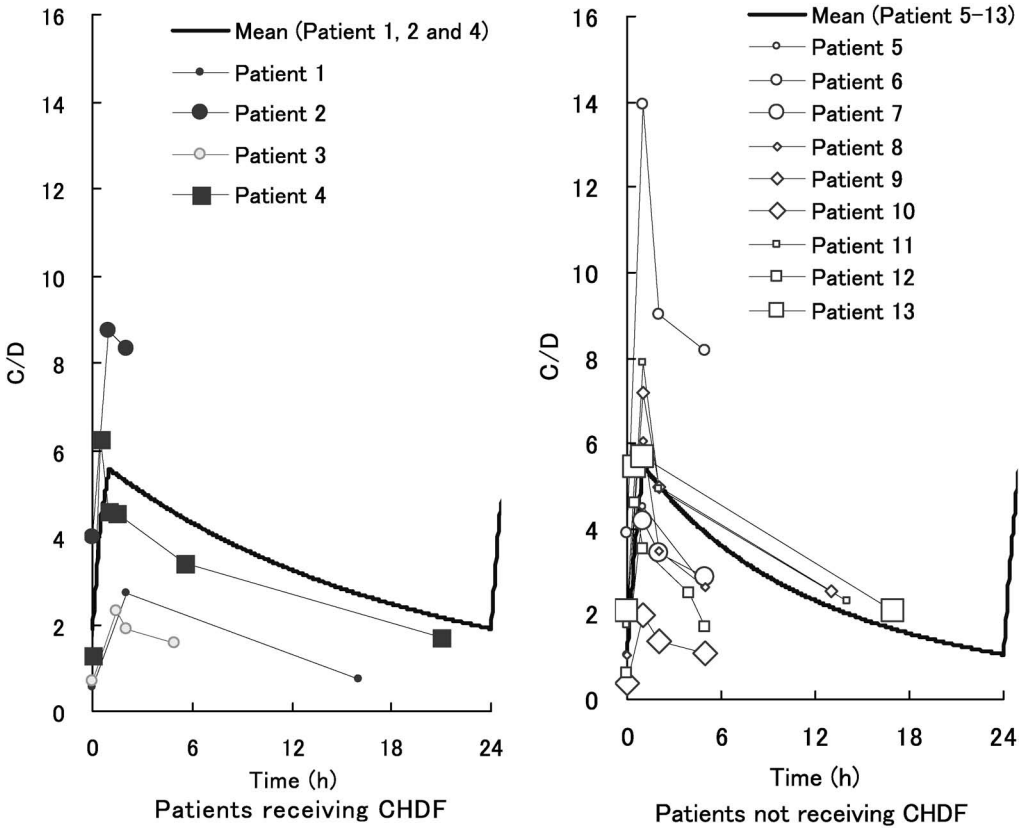

Fig. 3. Mean Serum Micafungin C/D-time Profiles of Patients Receiving (Patients 1, 2, and 4) and not Receiving (Patients 5–13) Continuous Hemodiafiltration

Each line represents the simulated curve calculated according to the one-compartment model using the parameters listed in Table 2. C/D: ratio of serum micafungin concentration to dose per body weight, CHDF: continuous hemodiafiltration.

DISCUSSIONS

Micafungin is a novel, semisynthetic lipopeptide antifungal agent in the echinocandin class. The pharmacokinetics of micafungin have been previously studied in healthy volunteers. It was reported that micafungin showed linear pharmacokinetics between 25 to 150 mg administration, and the mean ($\pm$ standard deviation) of Vdss and CL were 0.228 ± 0.016 l/kg and 0.197 ± 0.018 ml/min/kg, respectively.[8] In transplant patients, the area under the micafungin concentration-time curves was proportional to dose at doses up to 8 mg/kg/day.[9] The molecular weight and protein-binding rate of micafungin are 1292.3 and 99.8%, respectively.[8] Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an essential polymeric polysaccharide in the cell wall of many pathogenic fungi.[10,11] Moreover, micafungin has been demonstrated effective in the treatment of fungal infections and has shown no tolerability problems.[12] Fungal infections are still one of the main causes of complications and death in critically ill patients. CHDF has been used for the treatment of seriously ill patients with renal failure.[13] CHDF has appreciable effects on the pharmacokinetics of various drugs.[14] Drug properties may be altered by removal by continuous renal replacement in critically ill patients.[15] Therefore pharmacokinetic studies and the evaluation of the risk of exclusion of micafungin in critically ill patients treated by CHDF are important. However, data concerning the influence of CHDF on the pharmacokinetics of micafungin have not been evaluated. The aim of this study was to evaluate the pharmacokinetics of micafungin in critically ill patients treated by CHDF.

Extraction rate describes the capacity of a filter to remove a drug. The extraction rates obtained for micafungin suggest that CHDF does not effectively remove micafungin from blood. This might be expected considering the high degree of protein binding[16] of this compound. The CHDF filter permits the passage of small-to-medium-sized molecules

due to its relatively large pore size.

The CL obtained in patients receiving (patients 1–4) and not receiving (patients 5–13) CHDF was 1.4 l/hr and 1.4 l/hr, respectively. CL has been shown higher than 0.7 l/hr in healthy subjects.[8] The CL of micafungin was extremely lower than the hepatic serum flow rate. This result can be explained by the high protein binding of micafungin[8] and reductions of serum albumin and total protein in ICU patients. The variability of CL was large in patients receiving and not receiving CHDF; however, the distribution of CL was also equal between the patients receiving and not receiving CHDF as shown in Fig. 2. We observed clearance through CHDF to be 1.7 ± 1.5 ml/min under the condition where micafungin was not determined in blood cells, because the distribution of micafungin in blood cells has been reported only 32.2-35.1%.[17] This value was 7.2% of the CL in the patients receiving CHDF (Table 2). Therefore it was considered that the CL of micafungin was unaffected by CHDF. Micafungin is metabolized extensively in the liver; therefore extracorporeal excretion does not play a significant role. As shown in Fig. 3, no progressive difference in serum micafungin C/D-time profiles was observed between the patients receiving and not receiving CHDF.

In conclusion, these results show that CHDF does not affect the pharmacokinetics of micafungin. Therefore it is not necessary to adjust the micafungin dose in patients treated by CHDF.

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