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Pharmacokinetics-pharmacodynamics of micafungin in Japanese patients with deep-seated mycosis

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SUMMARY

The objective of this study was to describe the pharmacokinetic profile and investigate the effective concentration of micafungin in Japanese male patients with deep-seated mycosis. 66 patients were treated with i.v. micafungin 12.5-150 mg intravenously for up to 56 days. At this dose range, micafungin showed linear pharmacokinetics, and the mean values of C_{max} and C_{min} amounted to 3.16-12.9 μg/mL and 0.70-3.68 μg/mL, respectively. The mean value for the elimination half-life was 13.5 h (95 samples from 65 patients), and it remained almost constant over the dose range. In addition, the elimination half-life was not influenced by age, gender or weight, and was similar to that found in healthy subjects. The active metabolites M1 and M2 were detectable, but their exposure was lower than that of the unchanged drug. The pharmacokinetic–pharmacodynamics ob micafungin were then investigated. The overall clinical response rate against aspergillosis and candidiasis showed good results at a dose of 50 mg and over. The C_{max} and C_{min} at the latter dose amounted to 5.16 and 1.41 μg/mL, respectively.

In conclusion, micafungin showed linear pharmacokinetics at doses ranging from 12.5 to 150 mg, and the effective concentration was considered to be over 5 μg/mL as maximum level in Japanese patients with deep-seated mycosis such as candidiasis and aspergillosis.

INTRODUCTION

The echinocandins are lipopeptide compounds with potent anti-fungal activity (1). Micafungin (formerly known as FK463) was first introduced in Japan, then recently launched on the US market (2-4). Caspofungin is the compound of choice in the echinocandin class for use in the treatment of candidaemia and invasive candida infections in the US (5-6). However, at present these echinocandins drugs have poor bioavailability, are available in intravenous formulation only, and show linear pharmacokinetics after intravenous dosing (7). In two previous studies, the pharmacokinetics of micafungin in healthy male Japanese volunteers has been investigated at doses ranging from 25 to 150 mg. After repeated dosing, plasma concentrations reached a constant level on day 4. The mean±SD for drug disposition parameters, elimination half-life, total clearance and volumes of distribution at steady state were 13.9 ± 1.0 h, 0.228 ± 0.016 L/kg and 0.197 ± 0.018 mL/min/kg, respectively (8,9).

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The efficacy and safety of administering this drug to Japanese patients with aspergillosis or candidiasis have been demonstrated in a multi-center open-label phase II study of micafungin (10). This study concluded that monotherapy with micafungin seems to be both effective and safe, with an overall response rate for patients of 57% and 79% for aspergillosis and candidiasis, respectively.

The objective of this study was to demonstrate the linear pharmacokinetics of the drug, and to investigate the effective concentration of micafungin in a Japanese phase II study.

MATERIALS AND METHODS

Study design and patients

This multicenter, open-label clinical study was conducted at 41 sites in Japan, the details of which have been reported by Khono et al. (10). This investigation was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Pharmacokinetic sampling

Blood (approx. 1 mL, heparinized) was collected at 1-3 time points during the day, between 4 and 10 days after the initial administration of micafungin. Sampling took place 5 min before the completion of infusion whenever possible, 1 to 5 h after the completion of infusion, and before the start of infusion on the following day. When the dose was changed, the blood was collected in the same manner as described above.

Assay method

The plasma concentrations of micafungin and its metabolites (M1 and M2), which are also pharmacologically active against the experimental model of fungal infection (11), were determined using high-performance liquid chromatography (HPLC) with a fluorescence detector (12). The chemical structure of micafungin and its metabolites have been shown in Figure 1. The assay method adopted was validated by Japan Clinical Laboratories Inc. (Hyogo, Japan). Fifty microliters of human plasma were placed in a centrifuge tube to with the addition of 50 μL ethanol (or standard solution), 50 μL internal standard solution and 50 μL acetonitrile. The mixture was vortexed for 10 seconds and centrifuged at 10,000 rpm for 1 min. One hundred microliters of supernatant were transferred to a centrifuge tube using a transfer pipette, and added to 200 μL of 0.02 mol/L

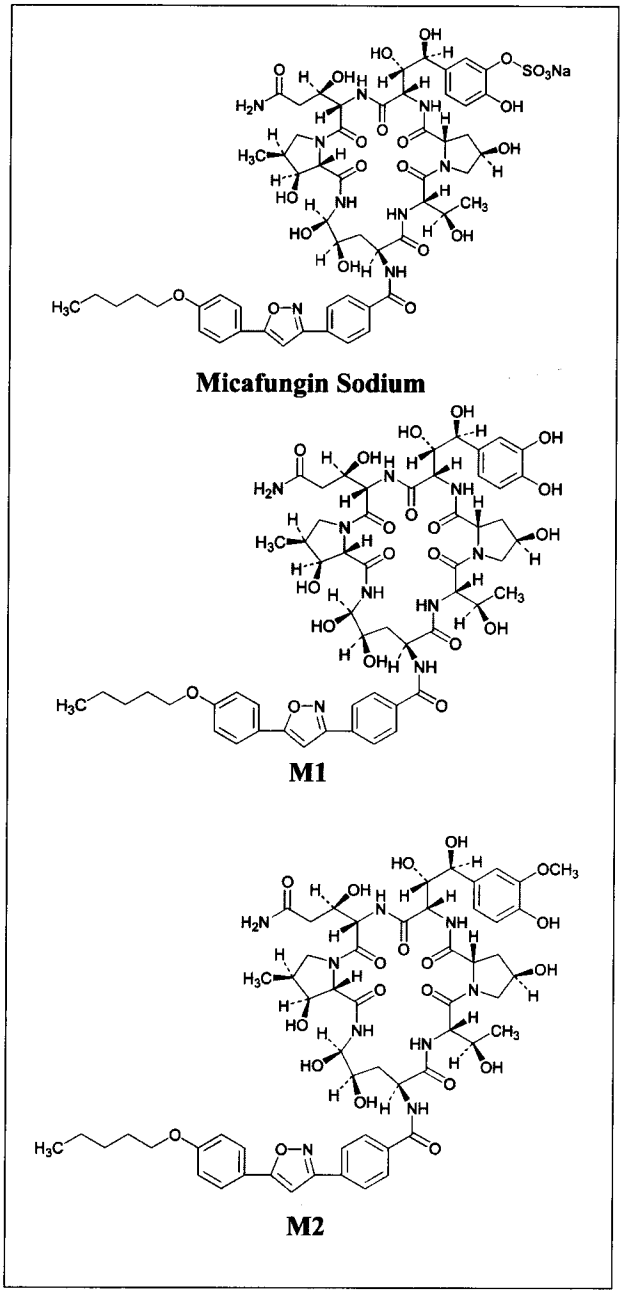

Fig. 1: Chemical structure of micafungin sodium and its metabolites M1 and M2. Micafungin appears to be metabolized by arylsulfatase to the catechol form (M1), while the methoxy form (M2) via M1 is generated by catechol-o-methyltransferase. Both metabolites are also pharmacologically active against the experimental infection model (11).

KH_2PO_4 solution. Thirty microliters of the mixture were injected into the HPLC system with an auto-sampler. A polypropylene insert vial was utilized. The separation of micafungin, M1, and M2 was carried out on a TSK gel ODS-80^{TM} column (4.6 mm I.D.×15 cm, ∅5 μm; Toso, Tokyo). For the HPLC conditions, the mobile phase

consisted of mixture of 0.02 mol/L KH_2PO_4 and acetonitrile (59:41), with a flow rate set at 1.0 mL/min and a column temperature adjusted to 50°C. The excitation and emission wavelengths for fluorescence detection were set at 273 nm and 464 nm (bandwidth 18 nm, gain 100), respectively. The lower limit for the quantification of micafungin and its metabolites were 0.05 μg/mL. The intra- and inter-assay precision and accuracy were found to be acceptable for the pharmacokinetic study.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters for micafungin and its metabolites were calculated from the drug concentration-time data by a non-compartmental pharmacokinetic model. Maximum plasma concentration (C_{max}), plasma concentration at the second time point (C_{2nd}), minimum plasma concentration (C_{min}) were assessed. The terminal elimination rate constant (k_e) was obtained from a log linear regression of the plasma concentration-time data. The elimination half-life ($t_{1/2}$) was calculated by the formula 0.693/ke. The relationship between the pharmacokinetic parameters and patient demographics (gender, age, body weight) was investigated by scatter plot.

RESULTS AND DISCUSSION

The aim of this study was to demonstrate the linear pharmacokinetics of micafungin, and to investigate the effective concentration in Japanese patients with deep-seated mycosis.

Patient characteristics are listed in TableI. 66 patients received a once-daily intravenous infusion of micafungin at dosages between 12.5 and 150 mg, for a minimum of 7 days and a maximum of 56 days. The infusion period was from 0.5 to 2.08 h. At least one blood sample was collected each day between 4–10 th day of the treatment period, and plasma concentrations of both micafungin and its active metabolites were determined for pharmacokinetic analysis. Blood sampling was repeated when the dose was altered. As a result, 107 items of concentration data were obtained from 66 patients, and the pharmacokinetic parameters (C_{max}, C_{min} and $t_{1/2}$) were calculated from the samples. The drug efficacy data from 65 patients, i.e. 42 subjects with aspergillosis and 13 with candidiasis, was derived from previous reports by Kohno et al. (10).

Table I: Patient characteristics in a clinical study of micafungin for the treatment of deep-seated mycosis in Japan.

No. of patients	66
Males	53
Females	13
Elderly (>64 years)	31
Non-elderly (<65 years)	35
Age (yr)	61.6±11.5 (26-77)
Body weight (kg)	48.5±8.1 (28-65.5)
Dose (mg)	12.5-150
Infusion time (h)	0.5-2.08
Total No. of samples analyzed	107

Table II presents the pharmacokinetic parameters and drug efficacy results. The mean values of C_{max} (CV%; number of samples) were 3.16 (21%; 4), 5.16 (30%; 34), 6.87 (32%; 32), 9.37 (-; 2) and 12.9 (19%; 12) μg/mL at 25, 50, 75, 100 and 150mg, respectively. Similarly, the values for C_{min} were 0.33 (21%; 3), 0.70 (47%; 20), 1.41 (35%; 34), 1.92 (40%; 30), 2.8 (-; 2) and 3.68 (23%; 12) mg/mL at 12.5, 25, 50, 75, 100 and 150 mg, respectively. These values increased almost in proportion to the dose. Figure 2 also shows the good linearity of C_{max} and C_{min} versus the dose administered. It was thus demonstrated that micafungin showed linear pharmacokinetics in this patient population.

The active metabolites, i.e. M1 and M2, were also evaluated. The mean trough concentrations of M1 were 0.112, 0.241, 0.353, 0.433 and 0.759 at doses of 25, 50, 75, 100 and 150 mg, respectively. M2 concentrations were detectable at 150 mg, and the values were in the range of 0.080 to 0.086 mcg/mL at a dose of 150 mg. These metabolite concentrations were considerably similar to those previously reported for healthy subject (9). The metabolite exposure was lower than that of the unchanged drug, indicating that the pharmacological activity of both metabolites must have a non-significant effect on therapy.

As regards drug efficacy, the overall clinical response rate showed good results at a dose of over 50 mg for the treatment of patients with aspergillosis and candidiasis. The C_{max} and C_{min} at the above mentioned dose were 5.16 and 1.41 μg/mL, respectively. In Figure 3, micafungin plasma concentrations were plotted against the overall clinical response (open circle: 'positive responce'; closed circle: 'negative responce') versus diagnosis: candidemia, disseminated candidiasis, esophageal candidiasis, invasive pulmonary aspergillosis, disseminated aspergillosis, chronic necrotizing pulmonary aspergillosis, and pulmonary aspergilloma. With regard to candidiasis, the patients with candidemia and esophageal candidiasis showed positive responses with 5 μg/mL at the C_{max} level.

The elimination half-life ($t_{1/2}$) of micafungin, with 95 values obtained from 65 patients, was calculated from second time points of plasma concentration and C_{min}, and the overall mean (±SD) was 13.5 (3.1) h. This remained almost constant over the dose range of 12.5 to 150 mg

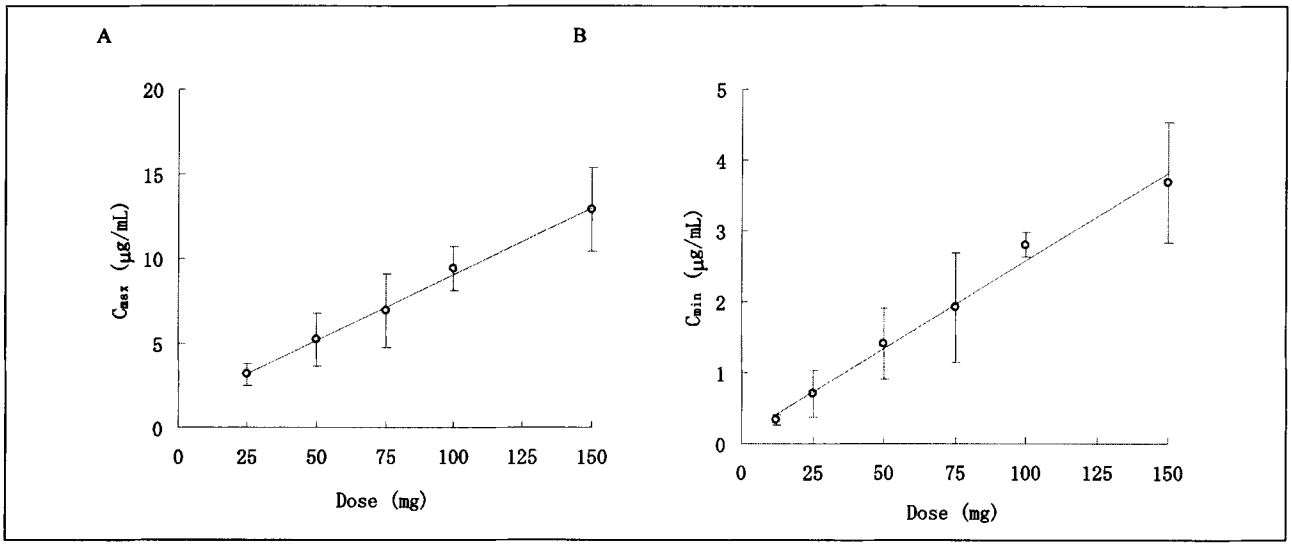

Fig. 2: Linear pharmacokinetics of micafungin at steady state in patients with deep-seated mycosis after a once-daily intravenous infusion of 12.5 to 150 mg of the drug. A: Maximum plasma concentrations (C_{max}), B: Minimum plasma concentrations (C_{min}). The symbol (○) and error bar indicate the mean and SD. The solid lines indicate the regression line of concentration versus dose (A: C_{max}=0.0784×dose + 1.21 (r^2=0.997), B: C_{max}=0.0247×dose + 0.107 (r^2=0.999)).

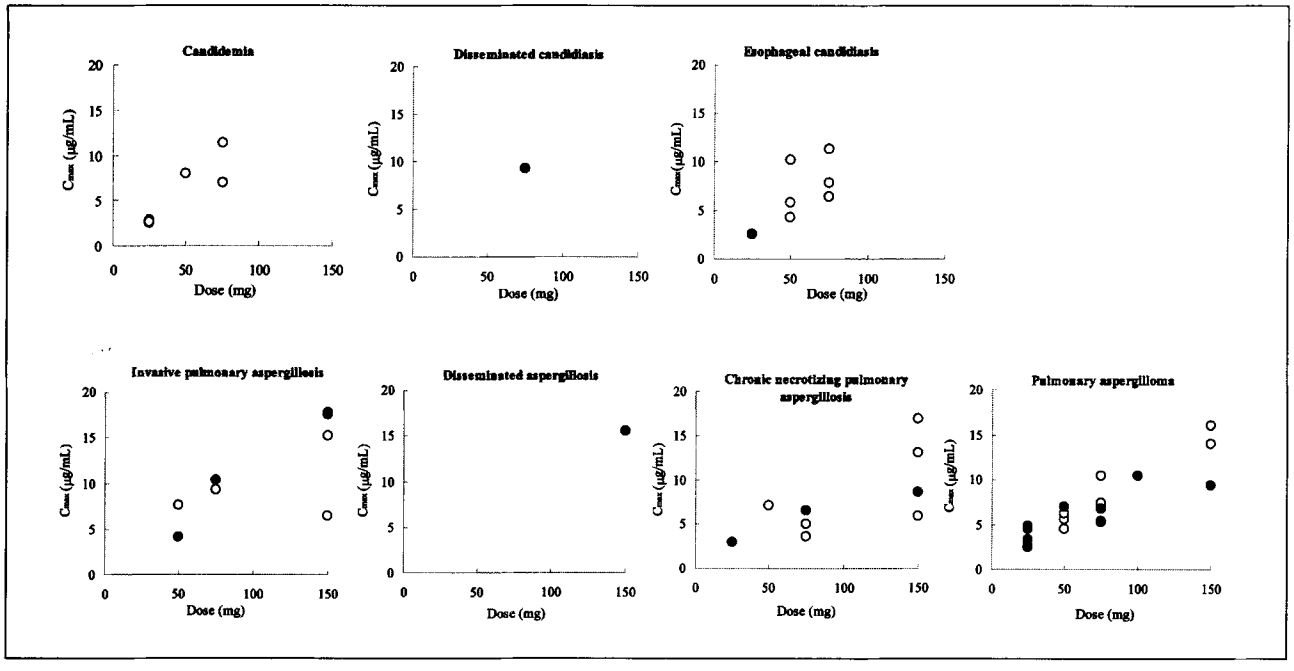

Fig. 3: Pharmacokinetic-pharmacodynamic relationship of micafungin in Japanese patients with deep-seated mycosis. Micafungin maximum plasma concentrations at steady state were plotted against overall clinical response (○: positive response, ●: negative response) by diagnosis; candidemia, disseminated candidiasis, esophageal candidiasis, invasive pulmonary aspergillosis, disseminated aspergillosis, chronic necrotizing pulmonary aspergillosis and pulmonary aspergilloma.

(Table II). Typical values for t1/2 in healthy subjects were 14.7 h (single-dose study) or 14.6 h (repeated-dose study). There were no differences found between healthy subjects and patients. To investigate age-dependent pharmacokinetics, $t_{1/2}$ values were rearranged by age group, i.e. elderly (over 65 years) or non-elderly (under 65 years), as shown in TableIII. Figure 4 shows the relationship between $t_{1/2}$ and patient backgrounds, age,

Table II: Plasma concentrations and pharmacokinetic parameters of micafungin following a 12.5- to 150-mg daily dose in Japanese patients with fungal infection. The value show the mean (±SD) and range (min.-max.). Samples: the number of detectable samples. NS: no sample (without sampling)

Dose (mg/day)	C_{max} (μg/mL)	C_{min} (μg/mL)	$t_{1/2}$ (h)	Overall clinical respons	
				A spergilbsis	Candidiasis
25	3.16 ± 0.67 (4)[1)]	0.70±0.33 (20)	13.3±2.4 (18)	2/7 (28.6%)[2)]	3/5 (60.0%)
50	5.16 ± 1.55 (34)	1.41±0.50 (34)	13.9±4.0 (33)	5/7 (71.4%)	4/4 (100%)
75	6.87 ± 2.17 (32)	1.92±0.77 (30)	13.2±2.5 (28)	8/14 (57.1%)[2)]	5/4 (80.0%)
100	9.37 ± 1.30 (2)	2.80±0.18 (2)	14.0±2.4 (2)	0/1	
150	12.87 ± 2.47 (12)	3.68±0.85 (12)	13.7±3.2 (12)	9/13 (69.2%)	

[1)] Mean ± SD (sam ples)
[2)] Responses/evaluable patients (percentage of responder)

weight and gender. The values for $t_{1/2}$ remained almost constant across age and weight between 10-20 h, and there was no obvious difference among males and females (Table III). These results agree with the finding of a previous pharmacokinetic study on healthy volunteers (13). Thus the pharmacokinetics of micafungin appears to be linear in this patients population with fungal infections.

Table III: Comparison of the elimination half-life between elderly and non-elderly or gender (male and female) following a daily dose of micafungin.

Background	No. of patients	No. of patients	$t_{1/2}$ (h) Mean (SD)
Non-elderly	35	56	13.4 (3.5)
Elderly	30	39	13.7 (2.5)
Male	53	79	13.4 (2.5)
Female	12	16	14.3 (5.2)

In conclusion, micafungin showed linear pharmacokinetics at a dose range of 12.5 to 150 mg, and the effective maximum concentration was considered to be over 5 μg/mL as maximum level, respectively, in patients with deep-seated mycosis such as candidiasis and aspergillosis.

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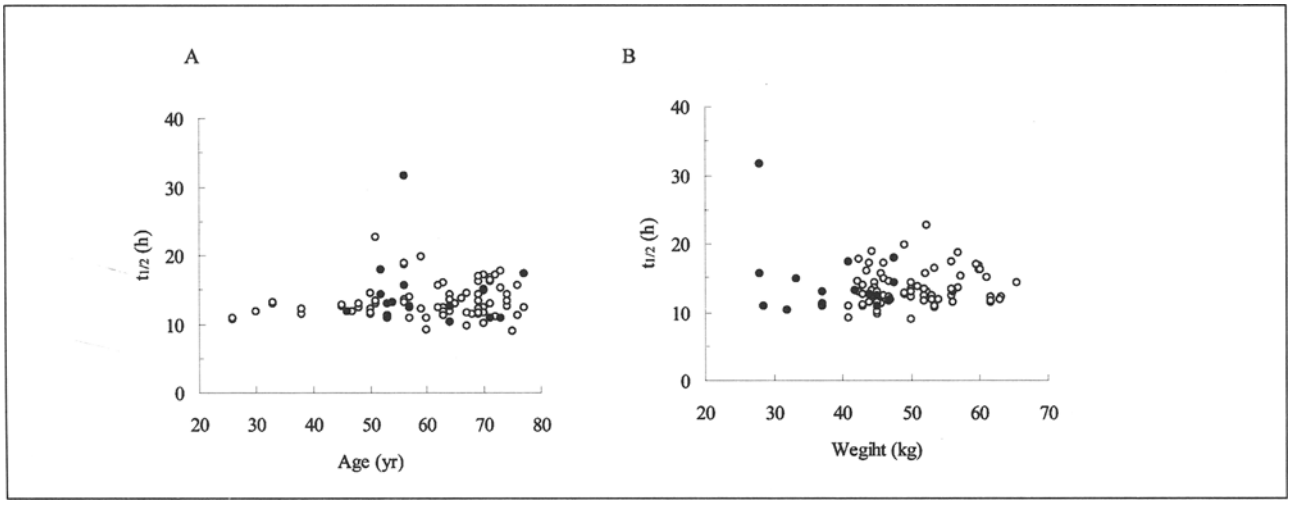

Fig. 4: Scatter plots for t1/2 of micafungin against background, age , body weight and gender (○: female; ●: male) in Japanese patients with deep-seated mycosis.

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