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Optimizing the Dosage Regimen of Micafungin against *Candida spp* in HIV Positive Patients with EC Based on Mote Carlo Simulation

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Abstract

The objective of our study was to explore the possibility of the antifungal efficacy of various micafungin dosage regimens against *Candida spp* in HIV positive patients with EC. According to pharmacokinetic/pharmacodynamics parameters of micafungin in HIV positive patients and MICs distribution of micafungin against *Candida spp*. in published studies, the dosage regimens of micafungin were 50, 100 and 150 mg QD iv. Monte Carlo Simulation analysed the probability of target attainment and cumulative fraction of response. The results showed that micafungin has good antifungal effect in treating HIV positive patients with EC when pathomycetes are *Candida albicans*, *Candida glabrata* or *Candida tropicalis*, in dosage at 100 mg QD and 150 mg QD.

Keywords

Monte Carlo Simulation, Micafungin, HIV Positive Patients, Esophageal Candidiasis

1. Introduction

In recent years, invasive fungal infections (IFIs) had been a significant factor in the morbidity and mortality of inpatients with invasive infections, especially in patients with immunodeficiency [1] [2]. The primary pathogenic fungi for IFIs are *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis* [1].

In patients with the human immunodeficiency virus (HIV) infection, eso-

phagal candidiasis (EC) is a common and severe complication, the incidence is 15% - 20%, and micafungin has shown great efficacy and tolerability in treating EC in HIV positive patients [3]. Micafungin is an echinocandin antifungal agent, which plays an antifungal role in selective inhibiting the synthase of β-(1,3)-D-glucan in the fungal cell wall [4] [5]. Micafungin mainly binds to albumin *in vivo*, the protein binding rate in plasma is 99% [6]. *In vivo*, micafungin is metabolized by the liver and excreted through the biliary tract, and mainly excreted through faeces [7]. Studies showed that micafungin has antifungal activities against *Candida spp.* both *in vitro* and *in vivo*, even for fluconazole resistance fungus [8] [9] [10] [11].

Monte Carlo simulation (MCS) is a useful tool for clinical treatment of dose selection, which can be sufficient to evaluate the effect of antifungal drugs and minimise the possibility of antifungal drug resistance. MCS has been used to assess the dosing regimens of micafungin in morbidly obese patients [12], critically ill patients with invasive fungal infection [13], critically burned patients with abdominal disease [14] and children [15]. In this study, MCS was used to optimise the micafungin dosage regimen of EC in HIV positive patients, to provide a basis for clinical application.

2. Materials and Methods

2.1. Pharmacokinetic Parameters

Pharmacokinetic parameters for micafungin in HIV positive patients with EC from the literature [3], PK data of intravenous micafungin in HIV-positive patients are shown in **Table 1**. Micafungin is a concentration-dependent antifungal drug with long-term aftereffects, and the antifungal effect is measured by $fAUC_{24h}/MIC$, PD target of *Candida spp.* is $fAUC_{24h}/MIC = 10$ [16], Free drug fraction f is 1%.

2.2. The Minimum Inhibitory Concentration (MIC) Data

The MICs distribution of *Candida spp.* is from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org). The data has shown in **Table 2**.

2.3. Monte Carlo Simulation

The probability of target attainment (PTA) is the target value of Pharmacokinetic/pharmacodynamic (PK/PD); the calculation formula is

Table 1. Pharmacokinetic parameters for micafungin in HIV positive patients.

PK parameters	50 mg/day (n = 20)	100 mg/day (n = 20)	150 mg/day (n = 14)
CL (mL/h/kg)	19.3 ± 5.9	19.8 ± 5.4	20.4 ± 5.5
$AUC_{0\text{-}24}$ (kg h/mL)	35.7 ± 8.9	74.5 ± 18.7	104.3 ± 26.3
C_{max} (μg/mL)	4.1 ± 1.4	8.0 ± 2.4	11.6 ± 3.1

Table 2. The MICs distribution of micafungin against *Candida spp.*

Species	n	MIC (μg/ml)												
		0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8
Candida albicans	1569	4	286	360	763	146	7	1	0	0	2	0	0	0
Candida glabrata	692	0	90	182	273	135	3	5	0	1	1	2	0	0
Candida krusei	483	0	1	0	4	26	185	215	37	9	2	4	0	0
Candida parapsilosis	743	0	0	0	3	1	0	1	35	113	332	244	14	0
Candida tropicalis	732	0	48	51	247	298	59	15	2	1	6	5	0	0

$fAUC_{24h}/MIC = (f \times dose)/(CL \times MIC)$ MCS simulated ten thousand patients through Crystal Ball software (version 11.1.2.4.600, Oracle). *CL* follows a logarithmic normal distribution, dose (mg) and f follow a uniform distribution, and MICs follows the custom distribution.

Cumulative fraction of response (CFR) describe the expected probability of the target value of the corresponding strain population, the calculation formula is $CFR = \sum_{i=1}^{n} PTAi \times Fi$. *PTAi* is probability of target for the specific MIC; *Fi* is the probability of every MIC distribution for an individual fungal sample, to achieve an excellent antifungal effect, PTA > 90% and CFR > 90% [12] [13] [14] [15].

3. Results

3.1. PTA Values

PTA values of micafungin against *Candida spp.* in HIV positive patients under different MICs distribution shown in **Figure 1**. The results showed that in dosage at 50 mg, the 5 *Candida spp* can reach the target when MIC is less than 0.032 μg/mL. In dosage at 100 mg and 150 mg, the 5 *Candida spp* can attain the goal when MIC is less than 0.064 μg/mL.

3.2. CFR

As the results are shown in **Table 3**, the effects of micafungin against *Candida krusei* and *Candida parapsilosis* are not sound, all CFR values cannot reach 90% in every dosage. The results also showed a good effect in micafungin against *Candida albicans* and *Candida glabrata*, all CFR values are higher than 90%. For *Candida tropicalis*, when the dosage of micafungin at 50 mg, CFR values below 90%, when the dosage of micafungin at 150 mg and 100 mg, the antifungal effect is proper, CRF values are higher than 90%.

4. Discussion

Micafungin is one of three currently available echinocandins in the treatment of Candidiasis, and the FDA recommends a dose of 100 mg QD for adult Candidiasis [17]. In HIV positive patients confirmed EC, no effect of race or gender

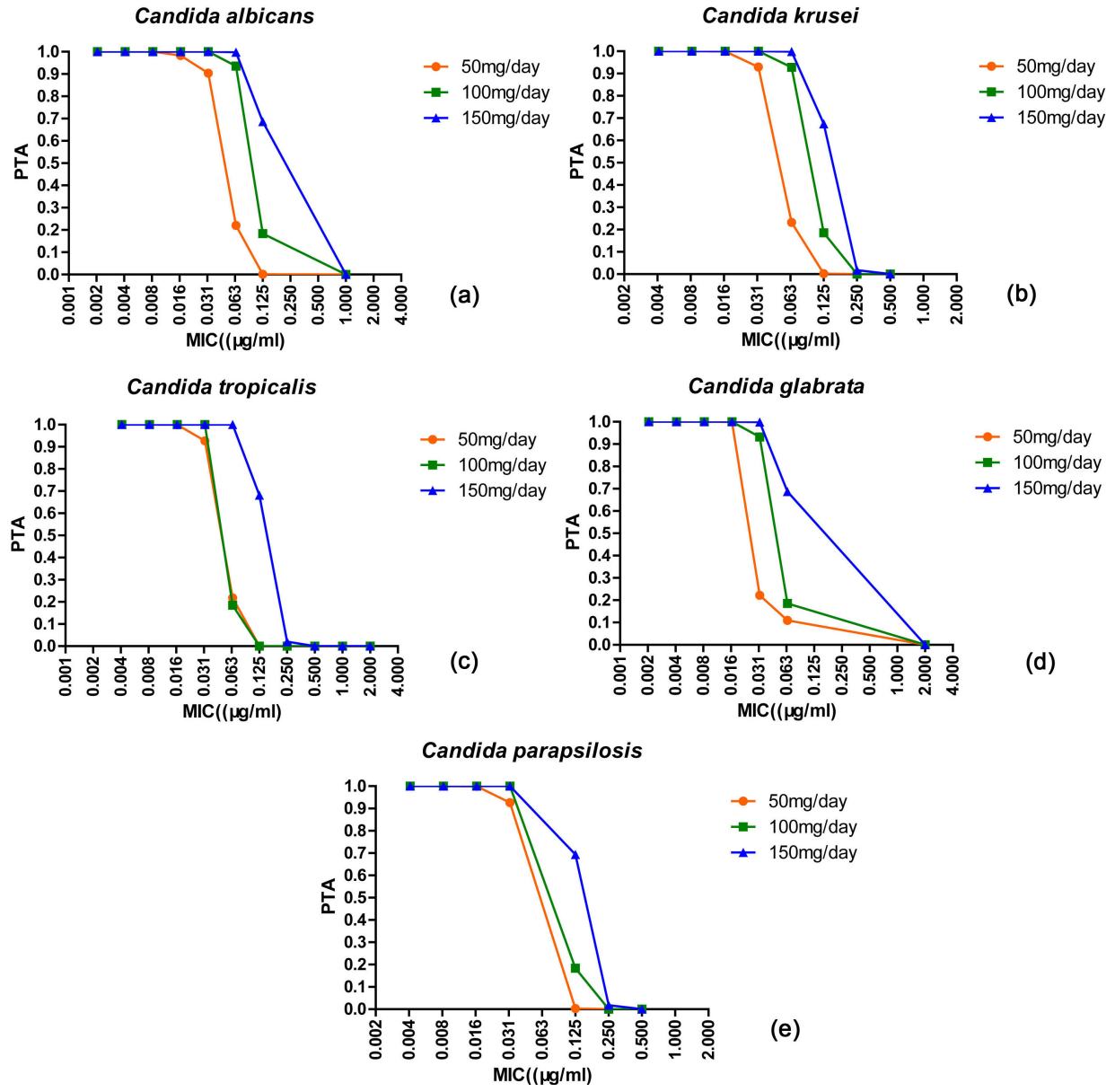

Figure 1. PTA of micafungin estimated at different dosage regimen against 5 *Candida spp*. in HIV positive patients with EC. (Key: 5 *Candida spp*. are *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis*. (a) to (e) show PTA values in of micafungin against 5 *Candida spp*. at different MICs in 3 dosage regimen: 50 mg/qd, 100 mg/qd and 150 mg/qd. (a) shows PTA values of *Candida albicans*, (b) shows PTA values of *Candida krusei*, (c) shows PTA values of *Candida tropicalis*, (d) shows PTA values of *Candida glabrata*, and (e) shows PTA values of *Candida parapsilosis*.)

Table 3. CFR (%) of micafungin against *Candida spp* in HIV positive patients with EC.

Species	CFR%		
	50 mg/day	100 mg/day	150 mg/day
Candida albicans	97.75	99.79	99.85
Candida glabrata	96.99	98.80	99.15
Candida krusei	15.01	50.23	74.84
Candida parapsilosis	0.53	0.57	0.71
Candida tropicalis	86.75	95.89	97.40

on the pharmacokinetics of micafungin [3].

Pharmacokinetics of micafungin in treating patients with EC was linear, predictable, which is similar to the published studies in healthy adults [3].

In our study, the antifungal effect of micafungin against different *Candida spp* in HIV positive patients with EC was quite different. For *Candida krusei* and *Candida parapsilosis*, micafungin has no antifungal impact, which is similar to the published studies in intensive care unit patients [18]. Our study also showed that micafungin against *Candida albicans*, *Candida glabrata* and *Candida tropicalis* has good antifungal effect in dosage greater than or equal to 100 mg, which is similar to FDA recommendation [17].

In this study, MCS used to carry out hypothesis analysis based on certain PK and strain data, which was beneficial to optimise the type and dosage of micafungin against *Candida spp* in HIV positive patients with EC. However, the research results of this paper also have some limitations, such as the MIC distribution of micafungin from some regions but not world-wide, so it can not reflect the development trend and change of the fungus in the future.

5. Conclusion

In summary, MCS is a simple, safe method to optimise dosage regimen according to the characteristics of fungi and PK/PD parameters. When pathomycetes are *Candida albicans*, *Candida glabrata* or *Candida tropicalis*, micafungin has good antifungal effect in HIV positive patients with EC, when pathomycetes are *Candida krusei* or *Candida parapsilosis*, other antifungal treatments are needed.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Kyriakidis, I., Tragiannidis, A., Munchen, S., *et al.* (2017) Clinical Hepatotoxicity Associated with Antifungal Agents. *Expert Opinion on Drug Safety*, **16**, 149-165.

[2] Enoch, D.A., Yang, H.N., Aliyu, S.H., *et al.* (2017) The Changing Epidemiology of Invasive Fungal Infections. *Methods in Molecular Biology*, **1508**, 17-65. https://doi.org/10.1007/978-1-4939-6515-1_2

[3] Under, N., Stevenson, P. and Baraldi, E. (2012) Pharmacokinetics of Micafungin in HIV Positive Patients with Confirmed Esophageal Candidiasis. *European Journal of Drug Metabolism and Pharmacokinetics*, **37**, 31-38. https://doi.org/10.1007/s13318-011-0063-8

[4] Chen, S.C., Slavin, M.A. and Sorrell, T.C. (2011) Echinocandin Antifungal Drugs in Fungal Infections: A Comparison. *Drugs*, **71**, 11-41. https://doi.org/10.2165/11585270-000000000-00000

[5] Carver, P.L. (2004) Micafungin. *The Annals of Pharmacotherapy*, **38**, 1707-1721. https://doi.org/10.1345/aph.1D301

[6] Muilwijk, E.W., Lempers, V.J.C., Burger, D.M., *et al.* (2015) Impact of Special Patient Populations on the Pharmacokinetics of Echinocandins. *Expert Review of Anti-Infective Therapy*, **13**, 799-815. https://doi.org/10.1586/14787210.2015.1028366

[7] Wasmann, R.E., Muilwijk, E.W., Burger, D.M., *et al.* (2018) Clinical Pharmacokinetics and Pharmacodynamics of Micafungin. *Clinical Pharmacokinetics*, **57**, 267-286. https://doi.org/10.1007/s40262-017-0578-5

[8] Maesaki, S., Hossain, M.A., Miyazaki, Y., *et al.* (2000) Efficacy of FK463, a (1,3)-beta-D-glucan Synthase Inhibitor, in Disseminated Azole-Resistant Candida Albicans Infection in Mice. *Antimicrobial Agents and Chemotherapy*, **44**, 1728-1730. https://doi.org/10.1128/AAC.44.6.1728-1730.2000

[9] Messer, S.A., Diekema, D.J., Boyken, L., *et al.* (2006) Activities of Micafungin against 315 Invasive Clinical Isolates of Fluconazole-Resistant Candida spp. *Journal of Clinical Microbiology*, **44**, 324-326. https://doi.org/10.1128/JCM.44.2.324-326.2006

[10] Pfaller, M.A., Boyken, L., Hollis, R.J., *et al.* (2008) *In Vitro* Susceptibility of Invasive Isolates of Candida spp. to Anidulafungin, Caspofungin, and Micafungin: Six Years of Global Surveillance. *Journal of Clinical Microbiology*, **46**, 150-156. https://doi.org/10.1128/JCM.01901-07

[11] Warn, P.A., Sharp, A., Morrissey, G., *et al.* (2002) *In Vivo* Activity of Micafungin in a Persistently Neutropenic Murine Model of Disseminated Infection Caused by *Candida tropicalis*. *Journal of Antimicrobial Chemotherapy*, **50**, 1071-1074. https://doi.org/10.1093/jac/dkf247

[12] Wasmann, R.E., Smit, C., Heine, R., *et al.* (2019) Pharmacokinetics and Probability of Target Attainment for Micafungin in Normal-Weight and Morbidly Obese Adults. *Journal of Antimicrobial Chemotherapy*, **74**, 978-985. https://doi.org/10.1093/jac/dky554

[13] Boonstra, J.M., van der Elst, K.C., Veringa, A., *et al.* (2017) Pharmacokinetic Properties of Micafungin in Critically Ill Patients Diagnosed with Invasive Candidiasis. *Antimicrobial Agents and Chemotherapy*, **61**, pii: e01398-17. https://doi.org/10.1128/AAC.01398-17

[14] García-de-Lorenzo, A., Luque, S., Grau, S., *et al.* (2016) Comparative Population Plasma and Tissue Pharmacokinetics of Micafungin in Critically Ill Patients with Severe Burn Injuries and Patients with Complicated Intra-Abdominal Infection. *Antimicrobial Agents and Chemotherapy*, **60**, 5914-5921. https://doi.org/10.1128/AAC.00727-16

[15] Xu, G.Q., Zhu, L.Q., Ge, T.Y., *et al.* (2016) Optimal Micafungin Dosage Regimens in Pediatric Patients with Invasive Candida Infection. *Chinese Journal of New Drugs and Clinical Remedies*, **35**, 482-486.

[16] Lepak, A.J. and Andes, D.R. (2015) Antifungal Pharmacokinetics and Pharmacodynamics. *Cold Spring Harbor Perspectives in Medicine*, **5**, a019653. https://doi.org/10.1101/cshperspect.a019653

[17] Wasmann, R.E., Muilwijk, E.W., Burger, D.M., *et al.* (2018) Clinical Pharmacokinetics and Pharmacodynamics of Micafungin. *Clinical Pharmacokinetics*, **57**, 267-286. https://doi.org/10.1007/s40262-017-0578-5

[18] Yang, Q.T., Wang, T.T., Xie, J., *et al.* (2016) Pharmacokinetic/Pharmacodynamic Adequacy of Echinocandins against Candida spp. in Intensive Care Unit Patients and General Patient Populations. *International Journal of Antimicrobial Agents*, **47**, 397-402. https://doi.org/10.1016/j.ijantimicag.2016.02.004