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Evaluation of Dosages Regimen of Fluconazole in Patients of Candidemia with Gender by PK/PD and Mote Carlo Simulation

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Abstract

Candidemia is one of the four most common nosocomial blood infections and is the most common hospital-acquired fungemia in a recent multi-institutional study from the US. The mortality of Candidemia can be up to 50%. Fluconazole is a triazole derivative widely used for the treatment of invasive candidiasis. It was recommended as first-line drugs for the treatment and prevention of mycoses. In our study, we aimed to optimise the dosage of fluconazole with gender against *Candida spp*. based on pharmacokinetic/pharmacodynamics (PK/PD) analysis. We collected the published data about pharmacokinetic parameters of fluconazole and the MIC distribution of *Candida spp.* on fluconazole. We decided to evaluate the gender between males and females with the pharmacokinetics of fluconazole. Using probability of target attainment (PTA) and cumulative fraction of response (CFR) as indexes, crystal ball software 11.1.2.4 was used for Monte Carlo simulation of different dosage regimens of different males and females. For *C. albicans*, *C. tropicalis and C. lusitaniae*, when doses of regimen are 100 mg IV, 200 mg IV and MIC was lower than 1 g/ml, PTA was higher than 90%. For *C. tropicalis*, each dosing regimen and MIC was less than 2 g/ml. PTA was higher than 90%. As C. glabrata, C. parapsilosis, C. krusei, C. guilliermondii for PTA with more than 90%, MIC of fluconazole 200 mg were less than 32 g/ml, 64 g/ml and 64 g/ml, respectively. For the different dosage regimens 100 mg IV and 200 mg IV of fluconazole for *Candida spp*., it is desirable that fluconazole dosage regimens take into account both the gender of the patient.

Keywords

Monte Carlo Simulation (MSC), Fluconazole, Candidemia, Gender

1. Introduction

Candida is the normal flora of the human body, usually parasitic in the normal skin, oral cavity, gastrointestinal tract, and genitourinary tract mucosa. Under normal circumstances, the body has a perfect defense system against Candida. When the normal bacterial community is maladjusted, the normal physiological barrier is destroyed and the human immunity is low due to various reasons, they can invade the human body and cause diseases, leading to opportunistic infections [1]. Candidiasis, the most common form of invasive candidiasis, is an opportunistic bloodstream infection caused by Candida, which can be cultured in the blood of loyal individuals. It occurs in those with immune deficiency, long-term immunosuppressive therapy, critically ill, or long-term use of broad-spectrum antibiotics [2] [3].

Fluconazole was introduced as a treatment for Candidiasis two decades ago and remained the most frequently prescribed drug for Candidemia [4]. Fluconazole can effectively inhibit the synthesis of ergosterol. It caused the loss of chromatin P-450 activation and phonogenic enzyme function, and the change of membrane permeability and death of fungal. Targeting fluconazole therapy to achieve predefined pharmacodynamic goals has been suggested as a means of optimising treatment of patients with Candidemia.

To maximize the likelihood of favorable clinical outcomes and minimize the probability of antimicrobial resistance, Monte Carlo simulation (MCS) is a computer simulation technology based on random numbers. Its basic principle is to randomly sample function distributions of different variables and substitute them into data models to obtain approximate solutions to research problems.

The method using the pharmacokinetic/pharmacodynamics (PK/PD) theory, the dynamic response can be drug in the body concentration-response relationship with aging. The optimal dose and administration scheme of antibacterial drugs were studied by the probability of target attainment (PTA) and cumulative fraction of response (CFR), so as to determine the optimal treatment scheme. To eliminate pathogenic bacteria, it can improve the success rate of treatment, and reduce adverse drug reactions and bacterial resistance [5] [6].

In this study, with the aid of PK/PD theory, the MCS model was applied to optimize the clinical administration scheme of fluconazole to *Candida spp.* with the population of different genders as the research object, in order to provide medication reference for clinical individualization.

2. Materials and Methods

2.1. Pharmacokinetic Parameters

Information regarding the pharmacokinetic parameters of fluconazole was obtained from published studies.

Information from studies that evaluated clinically relevant dosage regimens and provided the mean results for the pharmacokinetic parameters of interest with

Table 1. Pharmacokinetic parameters for fluconazole.

Parameter [7]	Han	Mongolian	Korean	Uygur	Hui
CL(L/h)	0.94 ± 0.18	1.09 ± 0.25	0.99 ± 0.19	1.02 ± 0.19	0.93 ± 0.26

corresponding measures of variability of areas under the concentration-time curve at steady-state (AUCs) were included. PK parameters of each administration regimen are shown in **Table 1**.

Estimates of pharmacokinetic parameters of fluconazole of subjects from five different ethnicities after a single oral administration of 200 mg tablet of fluconazole (n = 10 for each group).

Parameter [8] [9]	Male (mg)		Female (mg)	
	100	200	100	200
CL(L/h)	1.013 ± 0.043	1.07 ± 0.21	0.898 ± 0.028	0.92 ± 0.19

f = 1-PBs, plasma protein binding of fluconazole is 12% [10].

2.2. The Minimum Inhibitory Concentration (MIC) Data of *Candida spp.*

The MIC distribution of fluconazole against *Candida spp.* for seven species is derived from the Data from published articles [8] [9] [10] [11] (shown in **Table 2**).

2.3. Monte Carlo Simulation

MCS evaluates antifungal dosage regimens by integrating pharmacokinetic (PK) parameters, Minimum Inhibitory Concentration (MIC) distribution, and pharmacodynamics (PD) parameters. Crystal Ball (version 11.1.2.4.600, Oracle) software was used for Monte Carlo Simulation to obtain a probability of target attainment (PTA) and a cumulative fraction of response (CFR) for each dosing regimen of fluconazole. The PK/PD parameters of fluconazole were expressed in AUC/MIC ratio. The formula is *f* AUC24h/MIC > 55.2 [11], where CL follows a lognormal distribution, *dose* (mg) and *f* follow a uniform distribution, and MIC follows a custom distribution. CFR ≥ 90% is considered as the best plan.

3. Results

3.1. PTA Values

PTA Analysis of fluconazole in healthy adults for 7 *Candida spp.* was shown in **Table 1**. The results showed that PTA values were more than 90% for *C. albicans*, *C. tropicalis* and *C. lusitaniae* when MIC was less than 1 g/ml in each dosing regimen. For *C. tropicalis* each dosing regimen of fluconazole attained the PTA when MIC was less than 2 g/ml. As *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. guilliermondii* for PTA with more than 90%, MIC of fluconazole 200 mg were less than 32 g/ml, 64 g/ml and 64 g/ml, respectively (shown in **Figure 1**).

3.2. CFR

The CFR of different dosing regimens of fluconazole in a single dose of healthy adults were shown in Table 3. The results showed that fluconazole had an excellent antifungal effect in the treatment of *C. albicans* and *C. lusitaniae* with a CFR

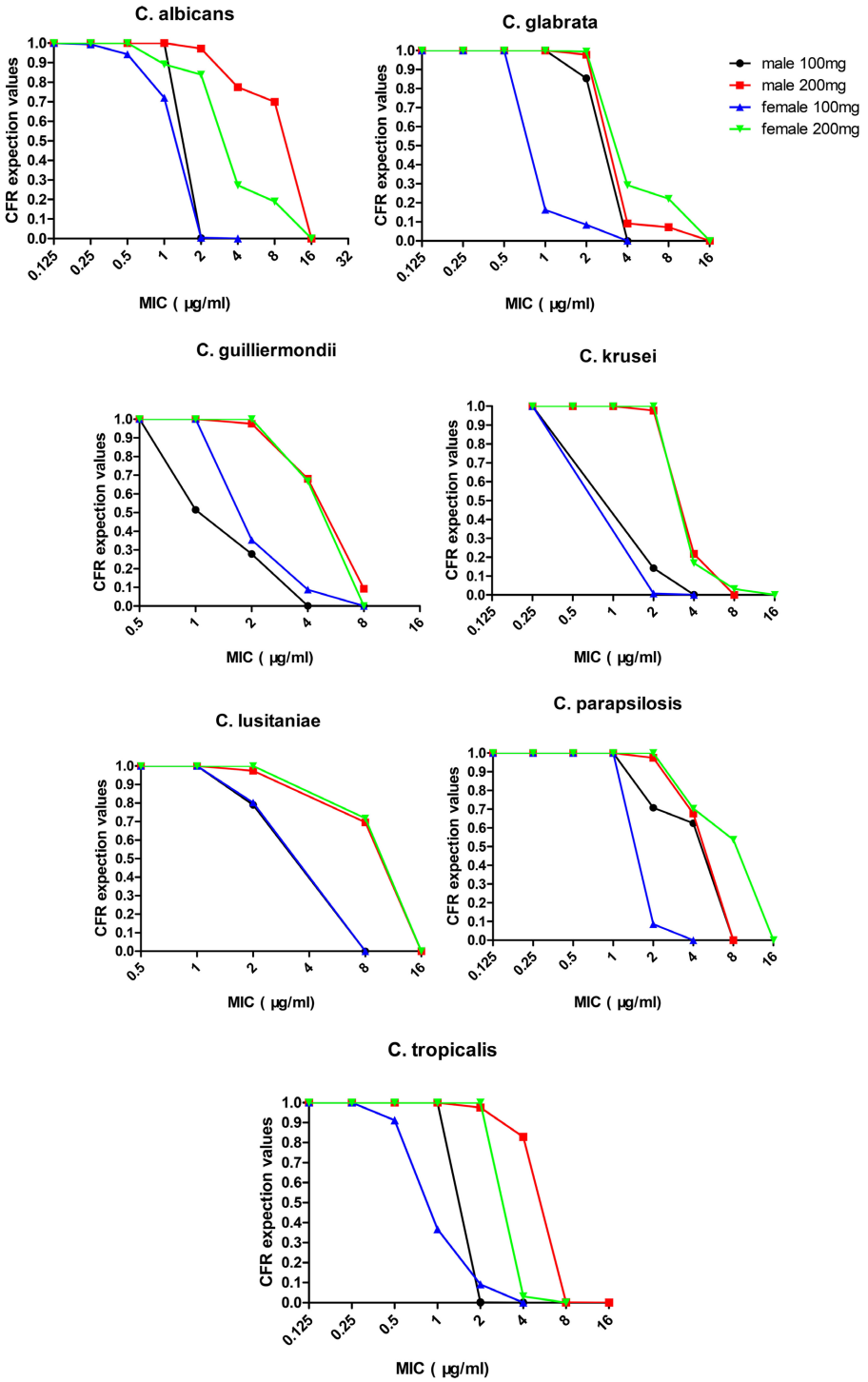

Figure 1. Probability of target attainment (PTA) of fluconazole at dose of 100 mg IV and 200 mg IV for treating Candida strains with different MIC values in patients with gender.

Table 2. Wild-type MIC distributions of fluconazole for seven species of Candida using CLSI broth microdilution methods [8].

Species	NO.	MIC (g/ml)										
		0.125	0.25	0.5	1	2	4	8	16	32	64	>64
C. albicans	8059	5159	2471	274	51	37	21	11	19	9	3	4
C. glabrata	2240	1	6	14	61	647	916	269	95	41	78	112
C. parapsilosis	2117	37	689	899	247	100	46	44	42	6	6	1
C. tropicalis	1771	344	826	379	137	57	11	10	6		1	
C. krusei	473		1			1	6	84	307	56	17	1
C. guilliermondii	170			5	32	81	41	4	3	3	1	
C. lusitaniae	190	43	54	63	18	5		2	1	3	1	

more than 90% with male and female. However, the dosage of fluconazole with CFR is more than 90% for *C. parapsilosis* and *C. tropicalis*is less in men than in women. And the dossage of fluconazole 100 mg IV in men and 200 mg IV in women for *C. parapsilosis* and*C. tropicalis*. The other Candida *spp*., such as *C. glabrata*, *C. krusei*, *C. guilliermondii*, of CFRs less than 90% of fluconazole 100 mg IV and 200 mg IV with different gender.

4. Discussion

Fluconazole, as a bis-triazole agent used in the treatment of fungal infections, with vaginal candidiasis being one of the commonest indications to fluconazole treatment [12], is time-dependent antifungal and has a long antibacterial afte-reffect, with a small amount of liver metabolism, prototype kidney excretion, low protein binding rate, wide tissue distribution, easy passage through the blood-brain barrier, good safety, etc.

Any species of *Candida spp.* more than 154 species can cause candidiasis, but only 10% of candida species are known to cause infections in human [13]. The most common causes of candidiasis disease pathogenic bacteria are: *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei*. *C. albicans* is the most common cause of candidiasis. Clinically, *C. albicans* is the most common, accounting for 50% - 70% of candida infection; virulence is also the strongest. However, since the 1990s, the incidence of candidiasis caused by non-candida albicans has increased. Recent investigations have found that nearly half of all candida cases are caused by non-Candida albicans [14]. It is worth noting that in recent years there has been a marked increase in infections caused by *C. glabrata*, and *C. krusei* [15] [16] [17]. In recent years, New pathogenic Candida species, for instance, *Candida auris* has emerged as a multidrug-resistant ascomycete yeast pathogen with the capacity for easy transmission between patients and hospitals, as well as persistence on environmental surfaces [18]. Most isolates were from males, which has gender difference.

In this study, according to PK/PD analysis, Monte Carlo Simulation was used

Table 3. CFR values (%) of 7 *Candida spp.* under different dosing regimens for different gender of fluconazole.

Species	Male		Female	
	100 mg	200 mg	100 mg	200 mg
C. albicans	98.71	99.45	98.19	99.12
C. glabrata	6.13	36.51	3.83	47.02
C. parapsilosis	93.13	94.70	88.83	95.80
C. tropicalis	95.20	98.85	88.72	98.44
C. krusei	0.24	0.69	0.21	25.93
C. guilliermondii	25.93	84.94	40.74	85.53
C. lusitaniae	95.76	96.98	95.79	97.07

to obtain the PTA and CFR values of fluconazole for 7 species of *Candida spp.* with different genders and dosages under the distribution of MIC values. The results showed that *C. albicans* and *C. lusitaniae* had good antifungal effect at 100 mg IV and 200 mg IV in different genders, while *C. parapsilosis* and *C. tropicalis*. were affected by gender. Good antibacterial effect was observed in males at different doses, while CFR < 90% was observed in females at 100 mg IV and good antibacterial effect was observed when the dose increased to 200 mg IV. In this study, Monte Carlo Simulation analysis showed that fluconazole had different antibacterial activities among different candida genera in both males and females. Miriam del C ect [8] studies showed that gender difference of fluconazole was related to badyweight, most likely because of differenesin total body water (TBW) between males and females. It provides a basis for subsequent clinical research and application.

5. Conclusion

In conclusion, the results of PK/PD modelling and Monte Carlo simulations suggest that fluconazole had a good antibacterial effect on *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae*. The best dosing for *C. albicans* and *C. glabrata* is 100 mg IV for male, but the dose of fluconazole for female is 200 mg IV. Fluconazole had a bad antibacterial effect on *C. glabrata*, *C. krusei*, *C. guilliermondii* across genders.

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Conflicts of Interest

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

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