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Analysis of Pharmacokinetic/Pharmacodynamic Parameters and Dosage Regimen of Posaconazole against *Candida* spp. and *Aspergillus* spp. Using Monte Carlo Simulation

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Abstract

Invasive fungal infections (IFI) have recently become increasingly more prevalent, resulting in an increased risk of morbidity and mortality. Both *Candida* spp. and *Aspergillus* spp. are major causes of IFI. In this study, we aimed to evaluate the cumulative fraction of response of various dosage regimens of posaconazole against nine *Candida* spp. and six *Aspergillus* spp. in both children and adults. Monte Carlo simulation (MCS) was performed to optimize selection of posaconazole dosage regimens. For children, a dosage regimen of 120 mg/m^2 posaconazole tid was sufficient to treat fungal infections caused by all six *Aspergillus* spp. and six of the nine *Candida* spp. (but was not effective against *C. glabrata*, *C. guilliermondii* and *C. krusei*). In contrast, a 400 mg dosage regimen of posaconazole bid achieved the target pharmacokinetic/pharmacodynamics (PK/PD) parameters against all six *Aspergillus* spp. and eight of the nine *Candida* spp. (but was not effective against *C. glabrata*) in the adults. Dosage regimens of 50 mg bid, 100 mg bid, or 200 mg bid were not effective. Posaconazole dosage regimens are likely to achieve their desired PK/PD targets against *Candida* spp. and *Aspergillus* spp. in both children and adults.

Keywords

Posaconazole, Monte Carlo Simulation, *Candida* spp., *Aspergillus* spp., Pharmacokinetics/Pharmacodynamics

1. Introduction

Invasive fungal infections (IFI) have recently become increasingly more preva-

lent, resulting in an increased risk of morbidity and mortality, mainly due to increasing numbers of immunosuppressed and cancer patients [1]. Both *Candida* spp. and *Aspergillus* spp. are major causes of IFI. *Candida* is the most common cause of IFI in critically ill and surgery patients. Invasive *Aspergillosis* has become more common in immunocompromised patients such as hematology-oncology patients, patients undergoing hematopoietic stem cell transplants, and solid organ transplant recipients [2] [3].

Although numerous antifungal agents have been used as prophylactics in high-risk patients, there are many limitations to these drugs. Amphotericin B deoxycholate is associated with infusion-related toxicity and dose-dependent nephrotoxicity. Furthermore, 5-fluocytosine and fluconazole have a narrow therapeutic index, whereas itraconazole has many clinically relevant drug adverse interactions. Echinocandins are only available as intravenous formulations, which hinders their clinical application [4]. Thus, these limitations have driven the need for new, more effective antifungal agents.

Posaconazole is categorized as a broad-spectrum triazole antifungal agent with potent *in vitro* and *in vivo* activities against a large number of clinically important yeasts and models [4] [5]. Posaconazole dissolves readily in lipids, is orally absorbed, and distributes significantly throughout the tissues. However, the dosage regimen can significantly influence the relative bioavailability of posaconazole, which can also be significantly increased by the administration of high-fat containing food [6] [7] [8]. The pharmacokinetics of posaconazole administered by oral suspension is characterized by low bioavailability, unpredictable plasma concentrations, and large inter-individual patient variability [9]. Assessing various dosage regimens is necessary to better understand differences in clinical response.

To maximize the likelihood of favorable clinical outcomes and minimize the probability of antimicrobial resistance, Monte Carlo simulation (MCS) is a very useful tool for determining the appropriate dose in most therapeutic areas [10] [11] [12] [13] [14]. MCS can be implemented to evaluate antifungal agent dosage regimens to integrate variables including pharmacokinetic (PK) parameters, minimum inhibitory concentration (MIC) distribution, and pharmacodynamic (PD) information. MCS is not only applied to many kinds of antimicrobial agents, but also applied to MIC breakpoints [15] [16] [17]. For example, Mouton JW *et al.* reveal the provisional breakpoint of BAL9141 is S (susceptible) < 4 mg/liter using MCS [16]. Doan TN *et al.* investigate the probability of target attainment (PTA) of various anidulafungin dosing regimens against *Candida* spp. in patients with acute leukaemia using MCS [15]. Therefore, we aimed to optimize selection of posaconazole dosage regimens by evaluating the probability of attaining target PD exposure against a wide range of clinical isolates of *Candida* spp. and *Aspergillus* spp. using MCS.

2. Materials and Methods

2.1. Pharmacokinetics

Information regarding the pharmacokinetic parameters of posaconazole was

obtained from published studies [18] [19]. Phase 1 studies were randomized and double-blind, and consisted of a placebo-controlled group and a parallel-group. Male and female volunteers ranging in age from 19 to 43 were randomly assigned to either receive treatment with posaconazole oral tablets (50 to 400 mg) or placebo tablets to be taken twice daily for 14 days [18]. Pharmacokinetic data of children aged 13 years or younger suffering from a hematologic malignancy were treated prophylactically with posaconazole oral suspension at a dose of 120 mg/m^2 three times daily, as reported by Vanstraelen K [19]. Information from studies that evaluated clinically relevant dosage regimens and provided the mean results for the pharmacokinetic parameters of interest with corresponding measures of variability of areas under the concentration-time curve at steady-state (AUCs) were included (Table 1).

2.2. Minimum Inhibition Concentration (MIC) Distribution of *Candida* spp. and *Aspergillus* spp.

The EUCAST MIC distribution website (http://www.eucast.org; last accessed March 13, 2017) was utilized to obtain MIC distribution data for *Candida* spp. (Table 2). MIC distribution data for *Aspergillus spp*. were gathered in five independent laboratories in Europe and the United States and tested using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M38-A2 document) (Table 3).

Table 1. Summary of posaconazole pharmacokinetic parameters following its administration in children.

Patient population	$AUC_{0\text{-}24}$ (mg·h/L)			
Children	120 mg/m^2 tid 20.5 ± 14.0[a]			
Adults	50 mg bid 8.29 (36)[b]	100 mg bid 21.78 (40)[b]	200 mg bid 31.11 (26)[b]	400 mg bid 73.11 (20)[b]

Note: $AUC_{0\text{-}24}$, area under the concentration-time curve from time zero to 24 h. [a]Value expressed as mean ± standard deviation. [b]The values in parentheses are the percentage coefficient of variance (CV%).

Table 2. Frequency distribution of the MIC of posaconazole for *Candida* spp. from the EUCAST MIC distribution website.

Species	n	MIC (μg/ml)												
		0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32
C. albicans	5297	3.15	64.73	21.92	7.02	1.59	0.64	0.36	0.08	0	0.06	0.21	0.25	0
C. dubliniensis	74	0	70.27	22.97	6.76	0	0	0	0	0	0	0	0	0
C. glabrata	1487	0.13	0.74	1.48	8.88	20.85	25.69	21.18	8.81	4.24	3.70	3.43	0.13	0.74
C. guilliermondii	153	0	2.61	15.03	32.03	24.83	16.34	4.58	1.31	1.31	0	0	1.96	0
C. kefyr	28	3.57	32.14	21.43	32.14	3.57	3.57	3.57	0	0	0	0	0	0
C. krusei	362	0	0.83	7.46	25.14	42.27	20.44	3.87	0	0	0	0	0	0
C. lusitaniae	43	0	79.07	18.60	0	2.33	0	0	0	0	0	0	0	0
C. tropicalis	1212	1.65	57.59	27.31	11.96	0.91	0.33	0.17	0	0	0.082	0	0	0
C. parapsilosis	754	0.93	47.61	33.55	8.49	2.12	1.72	0.40	0.40	1.33	1.33	0.93	1.19	0

MIC, Minimum Inhibitory Concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

Table 3. Frequency distribution of the MIC of posaconazole for *Aspergillus* spp.

Species	n	MIC (μg/ml)											
		≤0.01	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32
A. fumigatus	1647	6.38	25.62	26.11	21.31	13.96	5.83	0.73	0	0.06	0	0	0
A. flavus	321	0	9.97	41.12	26.17	17.45	4.05	0.62	0.62	0	0	0	0
A. terreus	330	0	5.76	15.76	27.58	38.18	12.42	0	0.30	0	0	0.30	0.91
A. niger	325	0	4.62	11.08	23.69	18.77	38.77	1.23	1.85	0	0	0	0
A. nidulans	129	0	13.95	11.63	6.98	34.88	17.05	13.18	1.55	0	0.78	0	0
A. versicolor	41	0	9.76	7.32	14.63	21.95	31.71	4.88	0	7.32	2.44	0	0

2.3. Monte Carlo Simulation

A pharmacodynamic study of posaconazole in a murine model of disseminated *Candidiasis* demonstrated that the free-drug ratio of AUC/MIC at 24 h ≥ 16.9 was the critical predictor of response to posaconazole therapy [20]. Furthermore, the free-drug posaconazole AUC/MIC ratio PD target at 24 hours was 1.09 for the wild-type and mutant isolates of *Aspergillus* in an *in vivo* model of invasive pulmonary *Aspergillosis* [21]. The free-drug AUC/MIC ratios of posaconazole at 24 hours for other pharmacodynamic targets of *Candidiasis* (6 - 30) and *Aspergillus* (0.4 - 2) were also displayed for each MCS.

The pharmacokinetic parameters were determined to as the lognormal distribution obtained with a mean and a percentage coefficient of variance (CV%). In the case of MIC, the data obtained from *Candida* spp. and *Aspergillus* spp. were assumed to follow a discrete distribution. Posaconazole protein binding was set at a constant value of 98% [6]. CrystalBall software (Fusion Edition, version 11.1.2.4.600, Oracle) was used for the Monte Carlo simulation consisting of 1000 subjects. The percentage of subjects who achieved the requisite pharmacodynamic exposure (fAUC$_{0\text{-}24}$/MIC) for each antibiotic dosage regimen/bacterial population combination is termed the probability of target attainment (PTA) [22]. The cumulative fraction of response (CFR) refers to the expected population PTA for a specific drug dose and a specific population of microorganisms [22].

The corresponding PTA of *Candida* spp. was determined at a fixed MIC value in the range of 0.008 - 32 μg/ml. For the calculation of PTA (*Aspergillus* spp.), MIC values were fixed from 0.01 to 32 μg/ml. Calculation of CFR was achieved using data based on the corresponding MIC distribution, whereby CFR values > 90% were considered optimal for a dosage regimen against a population of organisms.

3. Results

3.1. PTA Analysis

Figure 1 demonstrates the probability of PK/PD target attainment by MIC for posaconazole studied at the selected dosage regimens against *Candida* spp. and

Aspergillus spp. in children and adults.

The selected targets for *Candida* spp. were *f*AUC$_{0\text{-}24}$/MIC ≥ 16.9. Children (120 mg/m^2, tid) and adults (50 mg, 100 mg, 200 mg, 400 mg, bid) achieved PTA values of ≥90% for MICs ≤ 0.06, 0.03, 0.125, 0.25 and 0.5 μg/ml, respectively (**Figure 1(a)**). The chosen targets for *Aspergillus* spp. were *f*AUC$_{0\text{-}24}$/MIC ≥ 1.09. Posaconazole dosage regimens of 50 mg and 100 mg, tid, both resulted in PTA values of ≥90% for a 2 μg/ml MIC. Dosage regimens with children (120 mg/m^2, tid) and adults (50 mg, 400 mg, bid) resulted in PTA values of ≥90% for MICs ≤ 1, 0.5, and 8 μg/ml, respectively (**Figure 1(b)**).

3.2. CFR Analysis

Table 4 showed CFR assessment for different posaconazole dosage regimens. At a high *f*AUC$_{0\text{-}24}$/MIC value of 16.9 in *Candida* spp., the corresponding CFRs of *C. albicans*, *C. dubliniensis*, *C. lusitaniae*, and *C. tropicalis* were greater than 95%. Only *C. parapsilosis* had CFR values no higher that 90%. CFRs in *C. glabrata* were lower than 90% with the following dosage regiments: 120 mg/m^2, tid (38.04%); 50 mg, bid (14.46%); 100 mg, bid (43.35%); 200 mg, bid (57.49%); and 400 mg, bid (80.68%). CFRs for *C. guilliermondii* with a dosage regimen of 400 mg bid was greater than 90%. However, CFRs for *C. guilliermondii* with other dosage regimens varied from 51.17% to 89.89%. In *C. kefyr*, the CFRs of 120 mg/m^2, tid (92.70%); 100 mg, bid (94.39%); 200 mg, bid (96.43%); and 400 mg, bid (99.97%) were greater than 90%, but the CFR of 50 mg bid (86.52%) was less than 90%. Posaconazole dosage regimens in *C. krusei* achieved ≥90% CFR at 200 mg bid (94.80%) and 400 mg bid (99.99%), but 120 mg/m^2 tid (73.30%), 50 mg bid (39.15%), and 100 mg bid (83.15%) dosage regimens resulted in CFRs less than 90%.

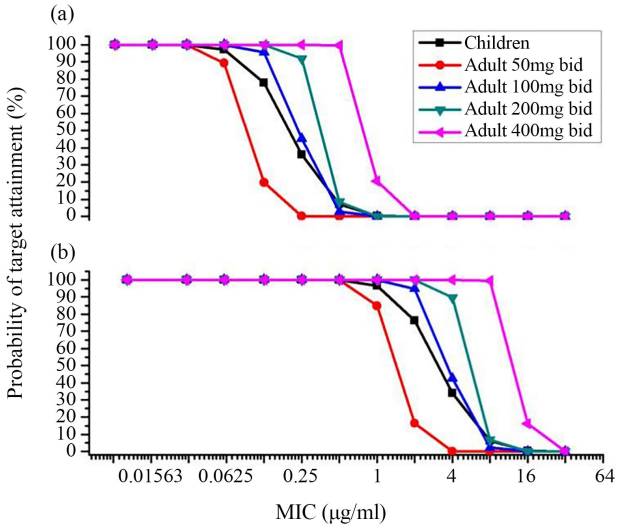

Figure 1. Probability of target attainment as a function of MIC for 10,000 simulated subjects being administered posaconazole. (a) The target was *f*AUC$_{0\text{-}24}$/MIC > 16.9 against *Candidiasis* spp.; (b) the target was *f*AUC$_{0\text{-}24}$/MIC > 1.09 against *Aspergillosis* spp.

Table 4. Cumulative fraction of response (CFR) expectation values (%) against nine *Candida* spp. and six *Aspergillus* spp. for each posaconazole dosage regimen in both children and adults.

Species	120 mg/m^2 tid	50 mg bid	100 mg bid	200 mg bid	400 mg bid
Candida spp.					
C. albicans	98.11	96.36	98.63	99.03	99.42
C. dubliniensis	99.79	99.25	99.99	100	100
C. glabrata	38.04	14.46	43.35	57.49	80.68
C. guilliermondii	74.34	51.17	80.89	89.89	95.67
C. kefyr	92.70	86.52	94.39	96.43	99.97
C. krusei	73.30	39.15	83.15	94.80	99.99
C. lusitaniae	99.47	98.12	99.89	100	100
C. tropicalis	99.01	97.38	99.52	99.74	99.92
C. parapsilosis	92.62	90.06	93.39	94.31	94.90
Aspergillus spp.					
A. fumigatus	99.92	99.81	99.96	99.99	100
A. flavus	99.82	99.38	99.96	100	100
A. terreus	99.90	99.72	99.98	100	100
A. niger	99.44	98.22	99.91	100	100
A. nidulans	98.40	95.89	99.15	99.27	99.99
A. versicolor	92.64	89.47	93.42	96.97	99.99

At a low *f*AUC$_{0\text{-}24}$/MIC value of 1.09 in *Aspergillus* spp., the corresponding CFRs of *A. fumigatus*, *A. flavus*, *A. terreus*, *A. niger* and *A. nidulans* were greater than 95%. The CFR of 50 mg bid in *A. versicolor* was 89.47%, but the remainder of dosage regimens resulted in CFRs greater than 90%.

To increase the clinical relevance of this study, several PK/PD targets for *Candida* spp. (from 6 to 30) and *Aspergillus* spp. (from 0.4 to 2) were analyzed by Monte Carlo simulation to simulate species-specific CFR expectation values (**Figure 2** and **Figure 3**). Increased PK/PD target values led to reduced CFR expectation values.

4. Discussion

In this study, we used MCS analysis to investigate the ability of posaconazole dosage regimens to achieve their requisite PK/PD target against nine *Candida* spp. and six *Aspergillus* spp. in both children and adults. Previous studies have demonstrated the efficacy of posaconazole against a variety of *Candida* spp. and *Aspergillus* spp. [23] [24] [25] [26]. The results of these simulations indicated that all of the dosage regimens simulated for children and adults were effective against five *Candida* spp. (*C. albicans*, *C. dubliniensis*, *C. lusitaniae*, *C. tropicalis* and *C. parapsilosis*) and five *Aspergillus* spp. (*A. fumigatus*, *A. flavus*, *A. terreus*,

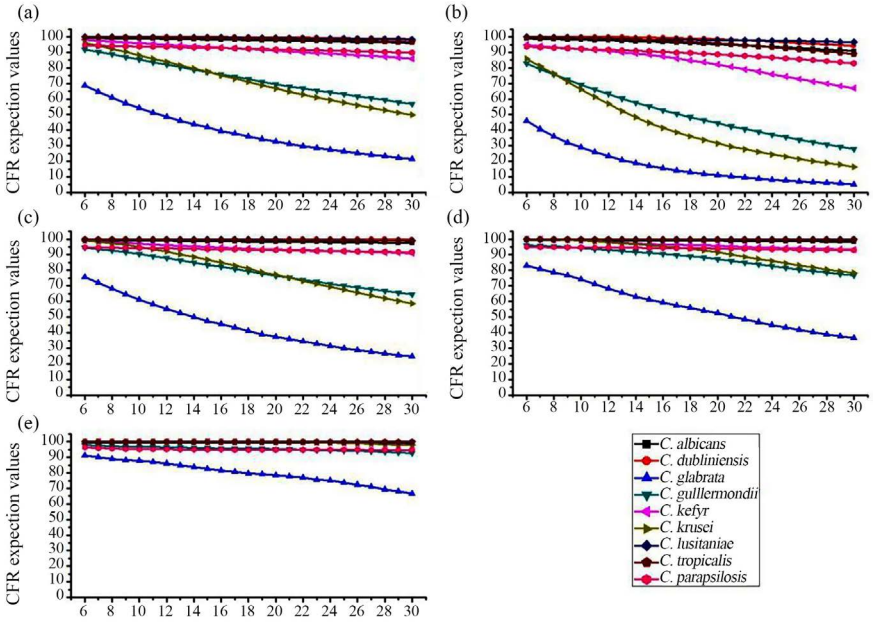

Figure 2. Cumulative fraction of response (CFR) expectation values of various posaconazole dosage regimens at various *f*AUC$_{0\text{-}24}$/MIC (free-drug area under the plasma concentration-time curve from zero to 24 h/minimum inhibitory concentration) targets against nine *Candidiasis* spp. (*C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. guilliermondii*, *C. kefyr*, *C. krusei*, *C. lusitaniae*, *C. tropicalis* and *C. parapsilosis*) in children and adults. The X axis label was *f*AUC$_{0\text{-}24}$/MIC targets. (a) 120 mg/m^2 tid; (b) 50 mg bid; (c) 100 mg bid; (d) 200 mg bid; (e) 400 mg bid.

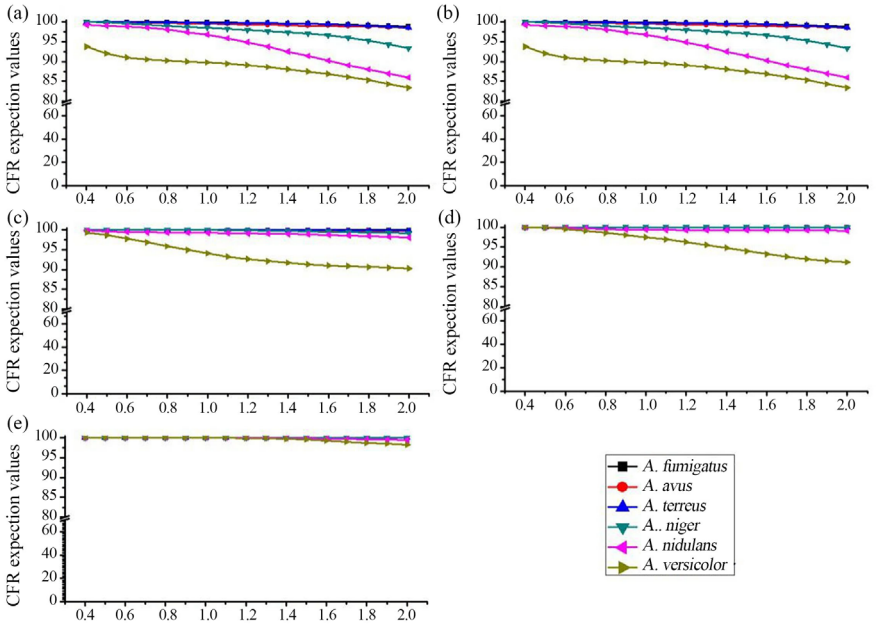

Figure 3. Cumulative fraction of response (CFR) expectation values of various posaconazole dosage regimens at various *f*AUC$_{0\text{-}24}$/MIC (free-drug area under the plasma concentration-time curve from zero to 24 h/minimum inhibitory concentration) targets against six *Aspergillus* spp. (*A. fumigatus*, *A. flavus*, *A. terreus*, *A. niger*, *A. versicolor*, and *A. nidulans*) in children and adults. The X axis label was *f*AUC0-24/MIC targets. (a) 120 mg/m^2 tid; (b) 50 mg bid; (c) 100 mg bid; (d) 200 mg bid; (e) 400 mg bid.

A. niger and *A. nidulans*). However, none of the simulated dosage regimens were effective against *C. guilliermondii* or *C. krusei* in children. Similarly, use of posaconazole doses of 50 mg bid or 100 mg bid was also ineffective against *C. guilliermondii* and *C. krusei* in adults. Increased doses (e.g. 200 mg bid) against *C. krusei* in adults resulted in CFR values ranging from 83.15% to 94.80%, demonstrating improved efficacy. This effect was not observed in *C. guilliermondii*. In addition, none of the posaconazole dosage regimens investigated achieved CFRs > 90% against *C. glabrata*. These results were consistent with MIC distributions that resulted in a CFR of 88.77% in *C. glabrata* (MIC range, 0.125 to 32 μg/ml).

Posaconazole is currently available as an oral formulation due to its poor aqueous solubility. Posaconazole oral suspension absorption is unpredictable and is often affected by concomitant medications and mucositis [27]. The compound achieves optimal exposure when administered in two to four divided doses with food or a nutritional supplement. For prophylaxis of invasive fungal infections, a 200 mg tid dose of posaconazole is recommended. In a previous study, pediatric patients aged 13 years or younger with hematologic malignancy received prophylactic posaconazole oral suspension at a dose of 120 mg/m^2 tid in comparison to the adult prophylactic dose of 200 mg tid. To achieve the same antifungal efficacy, pediatric patients require a relatively higher dose of posaconazole than adults. The need for a relatively higher dose in pediatric patients is due to a higher clearance rate of the drug per kilogram of body weight compared to adults [27]. Currently, the recommended dosage regimen of posaconazole is 400 mg twice daily with food for refractory oropharyngeal candidiasis or refractory invasive aspergillosis. In patients who cannot tolerate solid food, 200 mg posaconazole should be administered four times daily with a nutritional supplement [27]. These clinical dosage regimens are consistent with the results that found CFR > 90% (400 mg bid) against eight *Candida* spp. and six *Aspergillus* spp. in adults, and suggest that clinical use of this regimen is appropriate [28]. Dose adjustments are not necessary for patients with renal or hepatic dysfunction.

The appropriate PK/PD parameters have been extensively characterized for posaconazole. $AUC_{0\text{-}24}$/MIC is an important indicator of treatment efficacy. Numerous studies with antimicrobials have shown that an increased PK/PD index is necessary to be efficacious against organisms with reduced susceptibility to drug treatment. *In vivo* studies with posaconazole showed that free-drug $AUC_{0\text{-}24}$/MIC ranged from 6.12 to 26.7 (mean ± standard deviation, 16.9 ± 7.8) against *Candida* spp. and varied from 0.44 to 1.96 (mean ± standard deviation, 1.09 ± 0.63) against *Aspergillus* spp. [20] [21]. However, differences in PK/PD target values between *Candida* spp. and *Aspergillus* spp. should be considered when evaluating the efficacy of posaconazole treatment. In the present study, various PK/PD target values of *Candida* spp. (6 - 30) and *Aspergillus* spp. (0.4 - 2) were used to calculate CFRs of different posaconazole dosage regimens in

children and adults. FIG revealed that the probability of clinical success can be achieved for any given target values.

This is the first study to analyze the differences in CFR of posaconazole against *Candida* spp. and *Aspergillus* spp. in children and adults. However, there are some potential limitations to this study. First, the PK parameters of posaconazole were collected from a relatively small sample size of children and adults. In addition, an important weakness of the use of posaconazole oral solution is that there is not any data available regarding the PK parameters of intravenous or delayed-release oral formulations. Furthermore, this MCS analysis only considered serum pharmacokinetics, which could be useful for evaluation of bloodstream infections but not for other sites of infection such as tissue. Finally, antimicrobial use and local susceptibility should be considered when PK/PD modeling is applied to the predicted clinical outcome.

5. Conclusion

In conclusion, the results of PK/PD modeling and Monte Carlo simulations suggest that the currently approved high-dose regimen of posaconazole (400 mg bid) is sufficient to treat adults for fungal infections by *Aspergillus* spp. and *Candida* spp., with the exception of *C. glabrata*. In addition, we were able to determine that the dosage regimen of posaconazole (120 mg/m^2 tid) in children was most likely to attain the requisite PK/PD targets against *Aspergillus* spp. This was effective against *Candida* infections in children except *C. glabrata*, *C. guilliermondii*, and *C. krusei*. As such, further studies should focus on optimization of posaconazole dosage regimens to improve the probability of treatment success for specific fungal infections. Simulation by PK/PD modelling is a crucial tool with the potential to guide antibiotic therapy.

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Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Conflicts of Interest

The authors declare no conflict of interest.

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