We can do better: a fresh look at echinocandin dosing

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First-line antifungal therapies are limited to azoles, polyenes and echinocandins, the former two of which are associated with high occurrences of severe treatment-emergent adverse events or frequent drug interactions. Among antifungals, echinocandins present a unique value proposition given their lower rates of toxic events as compared with azoles and polyenes. However, with the emergence of echinocandin-resistant Candida species and the fact that a pharmacometric approach to the development of anti-infective agents was not a mainstream practice at the time these agents were developed, we question whether echinocandins are being dosed optimally. This review presents pharmacokinetic/pharmacodynamic (PK/PD) evaluations for approved echinocandins (anidulafungin, caspofungin and micafungin) and rezafungin (previously CD101), an investigational agent. PK/PD-optimized regimens were evaluated to extend the utility of approved echinocandins when treating patients with resistant isolates. Although the benefits of these regimens were apparent, it was also clear that anidulafungin and micafungin, regardless of dosing adjustments, are unlikely to provide therapeutic exposures sufficient to treat highly resistant isolates. Day 1 probabilities of PK/PD target attainment of 5.2% and 85.1%, respectively, were achieved at the C. glabrata MIC90 (0.12 mg/L) and MIC97 (0.06 mg/L) values, respectively, for these agents. However, evaluations of rezafungin demonstrated high probabilities of target attainment over 4 weeks of therapy (100%) after administration of a single-dose regimen at the MIC90 of 0.06 mg/L. This signals that although existing therapies are not optimal to treat resistant organisms, more potent new echinocandins (relative to achievable drug exposures) may be on the horizon.

Introduction

Clinicians today are provided a limited armamentarium regarding the therapies available to treat mycoses. Treatments are effectively limited to three drug classes: azoles, echinocandins and polyenes. Of these, the polyenes act by forming membrane pores through binding to ergosterol, a key structural component in fungal cell membranes. Thus, membrane permeability is increased, causing the leakage of intracellular potassium and other molecules. Azoles destabilize fungal cell membranes by preventing C-14α demethylation of lanosterol through binding to fungal cytochrome P-450 enzymes, resulting in decreased ergosterol production. However, the mechanisms by which these agents act present a double-edged sword. Non-specific binding of polyenes to cholesterol in mammalian cell membranes1 may result in drug-related toxicities. Development of therapies specific for fungi has been challenging given that, unlike bacteria, fungi are eukaryotic organisms. Thus, the targets for these agents are more likely to resemble those found in humans.3

Echinocandins are unique in that they target the cell wall. Given that this component is absent from mammalian cells, echinocandins are less likely to interact with human cells and therefore result in fewer toxic events as compared with azoles and polyenes. These agents reduce the integrity of fungal cell walls by disrupting glucan synthesis, their primary structural component, through inhibition of the 1,3-β-D-glucan synthase enzyme. These agents provide a safe and effective alternative to more traditional polyene and azole therapies. The first of these agents, caspofungin, received approval from the US FDA in 2001, which was later followed by approvals for micafungin and anidulafungin in 2005 and 2006, respectively. In the nearly two decades these agents have been available, no changes have been made to their recommended dosing regimens.4

Given that a pharmacometric approach to the development of anti-infective agents was not a mainstream practice at the time echinocandins were developed, the dosing of echinocandins may not be optimized for pharmacokinetics/pharmacodynamics (PK/PD). Moreover, the use of echinocandins5 has steadily increased and the prevalence of echinocandin resistance among Candida species,6–14 though still relatively rare, has also increased since these agents were introduced to the clinic. These trends are especially troubling in light of recent clinical studies which have indicated that treatment failures and patient mortality increase with caspofungin MICb–15,16 Thus, we are left questioning whether current dosing recommendations for these agents provide therapeutic drug concentrations in patients with infections due to resistant Candida. Herein, we will delve into this question and consider echinocandin dosing strategies, both traditional and novel. But we must first review how antimicrobial dosing regimens are derived.

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Dose fractionation: the first step towards regimen selection

In essence, an optimized dosing regimen is one which best balances the competing needs for high efficacy and low toxicity. Early investigations for dose selection are ideally performed preclinically. In vivo and in vitro infection models are utilized to characterize the relationship between drug exposures and fungal density (primarily measured as log10 cfu). Critical to our understanding of this relationship is recognizing the fact that not all antifungal agents exhibit the same patterns of fungicidal activity.17

Some drugs exhibit what is known as concentration-dependent activity, meaning that, as drug concentrations increase, so too do the rate and extent of pathogen killing.18 This pattern of activity is best captured by expressing drug exposures indexed to a pathogen’s degree of susceptibility to the agent in question. The PK/PD indices frequently assessed to evaluate such agents are the AUC/MIC and Cmax/MIC ratios. Conversely, for some drugs the rate and extent of bacterial killing are not increased over a wide range of drug concentrations. The activity of these agents is time dependent and their effects are largely dependent upon the time during which exposures remain above a target threshold. This is best captured by the percentage of time that drug concentrations remain above a pathogen’s MIC (%T>MIC). Collectively, the AUC/MIC ratio, Cmax/MIC ratio and %T>MIC are the three most common PK/PD indices used to characterize the relationship between exposure and efficacy.

Determining the PK/PD index most associated with efficacy for a given antifungal allows investigators to determine the magnitudes of these indices associated with different levels of bacterial reduction (i.e. PK/PD targets for efficacy). Such information can be used to identify PK/PD-optimized dosing regimens for development. The determination of the PK/PD index is made by conducting dose-fractionation studies, whereby fungicidal activity is evaluated by administering the same total dose of an agent over a multitude of dosing intervals. Multiple doses are administered in this manner to obtain a range of exposures.

Figure 1 shows data obtained from a dose-fraction study conducted by Andes et al.,19 in which neutropenic mice were infected with Candida glabrata and administered one of 20 anidulafungin dosing regimens. Total doses of 1.25, 5, 20, 80 or 320 mg/kg were administered over 96 h as one, two, four, or six divided doses (i.e. doses were given every 96, 48, 24 or 16 h, respectively).19 Using Hill-type models, relationships between the change in fungal density in homogenized tissue relative to baseline and the three PK/PD indices discussed previously were evaluated. As shown in Figure 1, these data demonstrated that fungal density was most closely associated with anidulafungin AUC/MIC and Cmax/MIC ratios, indicating that this agent exhibits a concentration-dependent pattern of fungicidal activity. The ideal regimen for this agent is one that optimizes anidulafungin exposures to maximize fungal killing while minimizing drug-induced toxicities.

Front-loading: answering the unexplored questions of efficacy

While data from dose-fractionation studies lay the foundation for the determination of target exposures and provide preliminary guidance for the selection of maintenance therapy (i.e. the data inform dosing frequency and magnitude), these studies are not designed to support the selection of the optimal duration of therapy. Moreover, they cannot assess what impact a loading dose will have on efficacy.

However, Okusanya et al.20 elegantly demonstrated how these factors impact efficacy of azithromycin in an evaluation of gerbils with Haemophilus influenzae middle ear infections. A front-loading experiment design was utilized, in which each animal was administered intermittent bolus doses to simulate human concentration–time profiles for one of three azithromycin dosing regimens containing the same total dose: (i) a 500 mg loading dose on Day 1 followed by 250 mg daily; (ii) 500 mg daily for 3 days; or (iii) a single 1500 mg dose on Day 1. Plasma concentrations and cfu counts were measured pre-dose and at 1, 2, 3, 4, 5, 6, 12, 24, 48 and 72 h to facilitate the creation of PK and PK/PD models. The observed and model-predicted data generated are shown in Figure 2. These data revealed that killing was most extensive and rapid following administration of the single azithromycin 1500 mg dose, suggesting that optimal outcomes could be achieved by administering a single dose of azithromycin, which maximizes exposures early in therapy and produces sustained

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**Figure 1.** Relationships between change in log10 cfu from baseline at 24 h and anidulafungin total-drug AUC:MIC ratio, Cmax:MIC ratio and %T>MIC. This figure is based on data from Andes et al.19
therapeutic concentrations to maintain antimicrobial activity. These analyses also served to demonstrate that, for some agents, the shape of the drug exposure is a determinant of efficacy.

**When does exposure shape matter?**

The hypothesis that the shape of the drug exposure can impact efficacy was also explored for the lipoglycopeptide oritavancin. In that evaluation, the authors provided support for the use of an oritavancin 1200 mg single-dose regimen for the treatment of acute bacterial skin and skin structure infections (ABSSSIs), which is now an approved treatment for such patients. This regimen was chosen with two considerations in mind, the first being that oritavancin demonstrates concentration-dependent bacterial killing. Second, oritavancin exhibits a very long terminal half-life of ~245 h. Azithromycin, for which the PK/PD index associated with efficacy is AUC:MIC ratio and which has a relatively short terminal half-life of 68 h, also exhibits these characteristics.

Consequently, without the use of a loading dose, it would take weeks for these agents to achieve steady-state concentrations. Conversely, when a front-loaded regimen is administered, the maximal rate and extent of bacterial killing can be achieved early in therapy, as previously shown with azithromycin.

The applicability of this concept to clinical practice was demonstrated through the results of a Phase 2 study in which 302 patients with ABSSSI were randomized to receive one of three oritavancin treatment regimens: (i) 200 mg daily for 3–7 days; (ii) 800 mg on Day 1 plus 400 mg on Day 5 (at the discretion of the treating physician); or (iii) a single 1200 mg dose on Day 1. Evaluation of data from patients across multiple analysis populations in this study revealed that clinical outcomes improved as the magnitude of exposures early in therapy increased. Data from two Phase 3 studies served to confirm the efficacy and safety of the single 1200 mg oritavancin dosing regimen in patients with ABSSSI.

The above-described data demonstrate that the shape of exposure impacts efficacy when an antibacterial agent exhibits a concentration-dependent pattern of bacterial killing and has a long half-life in plasma. Thus, such attributes together provide a basis for assessing candidate anti-infective agents for single or extended-interval dosing regimens. We can now enquire as to whether or not these same principles can be applied to antifungal agents.

**Rethinking echinocandin dosing**

As previously stated, the dosing of echinocandins has remained largely unchanged since these agents were brought to the clinic, whereas echinocandin-resistant *Candida* spp. have been increasingly emerging over this period. The most notable of these resistant pathogens has been *C. glabrata*, owing to this organism’s natural predisposition for expressing resistance mutations. As mentioned above, increases in *C. glabrata* MIC values have been associated with increases in treatment failures and mortality. Consequently, the consideration of treatment options for patients with these resistant organisms has become a priority.

Clinical studies have been conducted to establish differences in efficacy between approved caspofungin and micafungin dosing regimens and regimens with higher doses (70 mg followed by 50 mg daily versus 150 mg daily and 100 mg daily versus 150 mg daily, respectively). However, none of these studies demonstrated statistically significant differences in clinical outcomes between the standard and high-dose treatment regimens. These results are not surprising given that treatment differences are more likely to be seen when treating patients with isolates at the upper end of the MIC distribution, a population that is often too limited in sample size. When the MIC distributions for both agents were reported for these studies, the drug concentrations required to inhibit 90% of isolates (MIC) were ≤0.03 mg/L across all non-*C. parapsilosis* spp. These data suggest that exposures for both treatment regimens should have exceeded non-clinical PK/PD targets for the majority of isolates. However, the number of patients in clinical studies infected with pathogens with higher MIC values is often too limited to discriminate between dosing regimens. Given the limitations of the data described above, results of PK/PD target attainment analyses can be utilized to forecast the efficacy of different dosing regimen at fixed MIC values, including those that are higher but less frequently encountered.

Recent analyses that we conducted served to assess the adequacy of approved echinocandin dosing regimens for the treatment of patients with candidaemia in the context of contemporary *in vitro* surveillance data for *C. glabrata*. In that evaluation, Monte Carlo simulation was used to generate daily AUC values for simulated patients following the administration of 200 mg of anidulafungin followed by 100 mg daily, 70 mg of

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**Figure 2.** Plots of gerbil plasma concentration-time and changes in bacterial density superimposed over observed data and the model-predicted function for the rate of bacterial death.
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caspofungin followed by 50 mg daily, or 100 mg of micafungin daily. The simulated AUC values obtained from these analyses were evaluated relative to AUC/MIC ratio targets associated with net fungal stasis to assess the likelihood of achieving PK/PD targets associated with efficacy among highly resistant isolates. Relative to MIC$_{90}$ values, caspofungin and micafungin were likely to achieve therapeutic drug exposures in the majority of simulated patients, whereas anidulafungin was unlikely to achieve target exposures in the majority of simulated patients (Figure 3). However, when evaluating micafungin one dilution above the MIC$_{90}$ (0.06 mg/L), the percentage probabilities of PK/PD target attainment were less favourable, ranging from 10.3% to 49.9% over Days 1–14. These results are in contrast with caspofungin’s highly favourable percentage probabilities of PK/PD target attainment when evaluated relative to one dilution above the C. glabrata MIC$_{90}$ of 0.12 mg/L (100% across the entire 14 day treatment period). In response to these findings, PK/PD-optimized dosing regimens were proposed with the goal of providing therapeutic exposures early in therapy and maintaining these over a 2 week course of therapy. Increasing the anidulafungin dosing to 300 mg followed by 200 mg resulted in percentage probabilities of PK/PD target attainment across Days 1–14 improving from 0%–0.95% to 5%–54.3% for approved dosing at the C. glabrata MIC$_{90}$ of 0.12 mg/L. Similarly, improvements were observed when a micafungin regimen of 200 mg followed by 150 mg daily was evaluated (from 10.3%–49.9% to 85.1%–87.5%) at the C. glabrata MIC$_{97}$ of 0.06 mg/L. These results suggest that the current dosing regimens for caspofungin and micafungin are able to combat C. glabrata isolates up to and including the MIC$_{90}$ values for these agents. However, this was not the case for micafungin if the C. glabrata MIC$_{90}$ shifts upward even if only by one dilution. This is concerning given that resistance rates among C. glabrata spp. have been reported to be as high as 12% and acquired echinocandin resistance has been observed among various Candida spp., all of which support the need for new therapies.

One question that remains is whether the approved echinocandins can achieve greater efficacy when administered in larger quantities over extended intervals. It is well established that currently approved echinocandin agents exhibit a concentration-dependent pattern of fungal killing both in vivo and in vitro. Moreover, anidulafungin and caspofungin exhibit relatively long terminal half-lives in human plasma (40–50 h). Conversely, micafungin exhibits a more typical half-life of 13–17 h. However, despite micafungin’s short half-life relative to anidulafungin and caspofungin, murine disseminated candidiasis model studies have been conducted utilizing humanized single-dose and extended-interval dosing regimens. Although these studies showed promise for the use of single and extended-interval dosing of micafungin, clinical data evaluating such regimens are lacking.

However, recent work has been conducted to demonstrate the potential for single-dose administration of rezafungin acetate (previously CD101), a novel echinocandin in Phase 2 of development for the treatment of candidaemia and invasive candidiasis that has activity against Aspergillus and Candida spp., including azole- and echinocandin-resistant isolates. Lakota et al. evaluated rezafungin in a neutropenic murine disseminated candidiasis model, in which rezafungin 2 mg/kg was administered using either a single-dose, twice weekly, or daily regimen. Across these regimens, reductions in fungal density 168 h post-dose increased in parallel with the intensity of early exposures (Figure 4).

Figure 3. Distributions of free-drug plasma AUC:MIC ratio based on C. glabrata MIC$_{90}$ values (mg/L) for each respective FDA-approved echinocandin administered. The boxplot whiskers denote the 5th and 95th percentiles among simulated patients. Free-drug plasma AUC:MIC ratio PK/PD targets associated with net fungal stasis for each echinocandin are indicated by dashed lines.

Figure 4. Mean (bar) and range (error bars) change in log$_{10}$ cfu from baseline at 168 h after administration of 2 mg/kg rezafungin by a fractionation schedule. This figure is reproduced from reference 44 with kind permission from the American Society for Microbiology.

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same exposure was administered to each animal, but the magnitudes of fungal killing varied greatly, indicating that the shape of rezafungin exposure impacts efficacy. This should come as no surprise considering rezafungin, like other echinocandins, demonstrates a concentration-dependent pattern of fungal killing\(^4\) and exhibits a very long half-life in humans (133 h)\(^4\).

In order to translate these findings to humans infected with C. glabrata, we conducted PK/PD target attainment analyses utilizing the methodology previously employed in our evaluation of approved echinocandins\(^3\). A rezafungin free-drug plasma AUC\(^{0–168}\)/MIC ratio target associated with net fungal stasis of 0.5 was utilized\(^4\). Three dosing regimens were evaluated over 4 weeks: (i) 400 mg single dose; (ii) 400 mg weekly for 3 weeks; and (iii) 400 mg x 1 for Week 1 followed by 200 mg weekly for 2 weeks. Each of the dosing regimens evaluated performed well at the C. glabrata MIC\(_{90}\) of 0.06 mg/L\(^4\), including the single-dose 400 mg regimen. This regimen achieved percentage probabilities of PK/PD target attainment of 100% across Weeks 1–4 at this high MIC benchmark. In order to further evaluate these dosing regimens, PK/PD target attainment analyses were conducted utilizing a free-drug plasma AUC\(^{0–168}\)/MIC\(_{90}\) ratio target associated with a 1 log\(_{10}\) cfu reduction in C. glabrata of 2.94, and as described above for the net fungal stasis endpoint, all regimens achieved probabilities of PK/PD target attainment of 100% across Weeks 1–4 (Figure 5).

Concluding remarks

Herein, we described PK/PD target attainment analyses as a mechanism to evaluate labelled doses of approved echinocandins in the context of contemporary in vitro surveillance data and to 'pre-screen' revised regimens prior to conducting clinical assessments. The benefits of evaluating additional regimens were apparent in extending the utility of micafungin, which has been safely administered up to doses of 900 mg with limited occurrences of serious adverse events\(^4\), against C. glabrata up to the MIC\(_{90}\) value of 0.03 mg/L. However, the revised anidulafungin dosing regimen presented was not predicted to result in clinically meaningful increases in the likelihood of achieving efficacious drug exposures. Moreover, the doses included in this regimen, 200 and 300 mg, have only been assessed when administered intermittently over 48 and 72 h intervals, respectively\(^3\). Thus, the safety data associated with daily administration of these doses are lacking to date. Regardless, it is evident that these agents, regardless of dosing adjustments, are unlikely to provide therapeutic exposures to treat isolates with elevated MIC values (e.g. those one dilution above the MIC\(_{90}\)). Consequently, we evaluated rezafungin, a novel echinocandin, and conducted PK/PD target attainment analyses to demonstrate the potential to administer a single-dose regimen and provide exposures associated with efficacy for up to 4 weeks. This finding is significant in that such a regimen presents the opportunity to deliver drug exposures in a PK/PD-optimized manner, improve patient compliance and reduce the resources required for therapeutic drug monitoring over a long treatment period. In summary, existing echinocandin regimens can be PK/PD optimized to better balance the competing needs for high efficacy and low toxicity when treating patients with resistant Candida isolates. There may also be an opportunity in the future to utilize rezafungin and administer it as a single-dose regimen.

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Transparency declarations


Figure 5. Distributions of free-drug AUC\(^{0–168}\)/MIC ratios for C. glabrata based on MIC\(_{90}\). The boxplot whiskers denote the 5th and 95th percentiles among simulated patients. The rezafungin free-drug plasma AUC\(^{0–168}\)/MIC ratio PK/PD target associated with a 1 log\(_{10}\) cfu reduction in C. glabrata from baseline is indicated by dashed lines.
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