Pharmacokinetics and pharmacodynamics in the development of antifungal compounds

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Antimicrobial pharmacodynamics describe the relationship between drug exposure and treatment outcome. Pharmacodynamic studies provide information useful for dose level and dosing interval selection and for the development of in vitro susceptibility guidelines. Pharmacodynamic observations from animal model studies have proven useful for outcome predictions in the treatment of human infections. The strength of these predictions has been demonstrated most clearly for antibacterial drugs. Recent studies suggest that similar analyses may also be useful for antifungal drug development.

Keywords Antifungal, drug binding, pharmacodynamics, pharmacokinetics

Introduction

The field of antimicrobial pharmacodynamics examines the relationship between drug pharmacokinetics and antimicrobial activity or host toxicity [1••]. These investigations have been valuable for defining optimal antimicrobial dosing regimens and the validation and development of in vitro susceptibility breakpoints [2,3,4••,5]. The concepts encompassing this discipline were defined initially with antibacterial compounds [1••]. With the advent of standardized antifungal susceptibility testing, similar pharmacodynamic studies have been performed. Both in vitro and in vivo models have been able to demonstrate a strong correlation between drug dose, minimum inhibitory concentration (MIC) values of an organism and outcome [6-12,13••]. These investigations have been important for describing the relative potency of antifungal drugs against a number of important pathogens. More recent in vivo pharmacodynamic investigations have examined the relationship among drug dose, dosing interval, MIC values and treatment outcome to define the specific pharmacodynamic parameter and parameter magnitude predictive of antifungal drug activity.

Pharmacokinetic considerations

A wide variety of pharmacokinetic variables are considered in the preclinical development of anti-infective compounds. One goal of these pharmacokinetic investigations is to characterize the time-course of antifungal concentrations at the site of infection in relation to treatment efficacy. In addition, these studies are useful for examining relationships between drug concentration, drug toxicity and antimicrobial activity or host toxicity [1••,20,21]. Recent studies with the triazole antifungals have similarly demonstrated a relationship between the degree of protein binding and in vivo efficacy [17,18].

Animal model studies are frequently utilized to determine pharmacokinetics in serum, urine and cerebrospinal fluid (CSF). For antibacterial compounds, there has been a strong association between drug penetration into the CSF and treatment efficacy in animal infection models [14]. However, for antifungal drugs, this relationship has not been as strong [15]. Studies with several compounds, such as the polyene antifungals, have demonstrated excellent in vivo activity in the therapy of central nervous system infection despite the finding of minimal CSF drug penetration [16]. More recent experiments with drugs from the polyene class suggest that in vivo activity is better predicted by brain rather than CSF concentrations. Studies examining the impact of the penetration of anti-infective compounds into the urine have similarly found a poor relationship between these concentrations and the efficacy in renal infections [17,18]. Several investigators have suggested that outcome may be better predicted by renal parenchymal concentrations for the treatment of these hematogenous pyelonephritis infections. Very few studies have examined urine concentration and in vivo efficacy utilizing an ascending infection model of cystitis.

In addition, end organ tissue homogenates of animal lungs, liver, spleen and brain are often utilized to estimate drug penetration into these infection sites [13•]. However, tissues consist of two separate compartments that are intermixed during homogenization. Drugs often vary in distribution in the intracellular and the interstitial compartments. The intracellular compartment consists of a much larger volume than the interstitial compartment. Thus, tissue homogenate measurements can often either underestimate or overestimate drug concentrations at the site of infection depending on how much of the drug distributes in the intracellular compartment. With few exceptions, the primary tissue compartment of infection is the interstitial compartment. Numerous investigations have demonstrated that serum drug concentrations provide an accurate estimate of interstitial concentrations [19•]. In addition, most studies have demonstrated a strong relationship between serum pharmacokinetics and in vivo efficacy at a variety of infection sites other than the central nervous system. Very few studies have examined the relationship between organ homogenate drug concentrations and in vivo treatment efficacy, and these investigations have not demonstrated a superior predictive relationship.

Evaluation of anti-infective drug binding to serum proteins is another pharmacokinetic factor that has been shown to be an important predictor of in vivo efficacy [20]. Protein binding can restrict tissue distribution, delay drug elimination and reduce antimicrobial activity. Numerous studies with antibacterial compounds have demonstrated that only the free or unbound drug fraction is available for antimicrobial activity [1••,20,21]. More recent studies with the triazole antifungals have similarly demonstrated a relationship between the degree of protein binding and in vivo efficacy [17,18].
Pharmacodynamic patterns of activity
Both in vitro and animal model studies have examined the impact of antibiotic drug concentration on the killing of an organism over time, or on the time course of activity [1••]. Two factors define the ‘time course of antimicrobial activity’. The first is the impact of drug concentration on the rate and extent of organism killing. When antimicrobial killing is increased by increasing drug levels, the pattern of activity is referred to as ‘concentration dependent’. Concentration-dependent activity has been observed with drugs from the polyene and echinocandin antifungal classes [7,22•,23]. With some drugs, however, antimicrobial activity is not enhanced by increasing drug concentrations, but can be enhanced by prolonging the duration of exposure. This pattern of activity is referred to as ‘time-dependent’. Drugs from the triazole class and flucytosine produce ‘time-dependent activity’, also referred to as ‘concentration-independent activity’ [6,8,24].

A second factor important for defining pharmacodynamic activity is the organism growth dynamics following drug exposure [25,26]. With some antimicrobial drug classes, organism growth continues to be suppressed after the antimicrobial is no longer present at levels defined as necessary for drug activity (the MIC). This period of growth suppression is called the post-antibiotic effect (PAE). Studies with the polyenes, echinocandins and triazoles have demonstrated prolonged persistent growth inhibition following in vivo drug exposures [6,7,10,23]. In studies with flucytosine, however, only modest periods of growth suppression have been observed [8].

Antifungal time course studies in vivo have identified three combinations of these two factors (Table 1): (i) concentration-dependent killing and prolonged PAE with amphotericin B and the echinocandins; (ii) time-dependent killing and short or no PAE with flucytosine; and (iii) time-dependent killing and prolonged PAE with the triazoles.

Pharmacodynamic parameter predictive of efficacy
Three pharmacodynamic parameters describe the association between antimicrobial dosing and treatment effect (Figure 1) [1••,19•]. These parameters include the percentage of time that serum levels exceed the MIC (t > MIC), the peak serum level in relation to the MIC (peak/MIC), and the area under the serum concentration curve in relation to the MIC (AUC/MIC). However, analyses of treatment outcome from most animal models and clinical trials are rarely able to discern which pharmacodynamic parameter is better predictive of outcome or efficacy. Many of these investigations may consider several dose levels, but most often consider only a single dosing interval. The inability of these studies to make this distinction is due to the strong inter-relationship among the pharmacodynamic parameters. With each dose level increase, a similar increase in the AUC, peak level and the t > MIC is observed. In order to discern between these parameters, studies must utilize dosing regimens that limit these inter-relationships. This is most easily accomplished by varying not only the dose level, but also the interval of dosing, eg, with one dosing regimen, the 24 h total dose could be administered 4 times/day (eg, 100 mg/kg/24 h total dose, 25 mg/kg every 6 h). For another regimen, this same total dose could be administered in a single dose (eg, 100 mg/kg/24 h total dose, 100 mg/kg every 24 h). The first regimen will have a lower peak level, but a longer %t > MIC and the 24 h AUC between the two regimens will be relatively similar. Studies using dose fractionation with four to six dosing intervals are usually able to determine which of the three pharmacodynamic parameters correlates with in vivo activity.

Numerous studies with antibacterial drugs have demonstrated that the specific parameter predictive of activity varies for different drug classes, but is the same for drugs within a class [1••]. Each of the pharmacodynamic parameters is associated with one of the time courses of antimicrobial activity patterns described above (Table 1). For drugs that demonstrate time-dependent killing and short or no PAE, drug dosing is optimized by prolonging the duration of drug-organism exposure. The parameter that reflects this exposure is the t > MIC. Antimicrobials are often administered at lower doses but dosed more frequently to take advantage of this pattern of activity. Studies examining the pharmacodynamics of flucytosine demonstrated that %t > MIC was the most predictive of treatment outcome [8]. For drugs exhibiting concentration-dependent killing and long PAE, antimicrobial efficacy is optimized with large infrequent doses. The pharmacodynamic parameters that represent this type of dosing are the peak/MIC and the AUC/MIC. The peak/MIC parameter describes the pharmacodynamic activity of both the polyenes and echinocandins [7,23]. The final pattern of drug activity is characterized not only by concentration-independent killing, but is the same for drugs within a class [1••].

Table 1. Antifungal pharmacodynamic characteristics.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Concentration-dependent</th>
<th>Time-course activity</th>
<th>PAE</th>
<th>Pharmacodynamic parameter</th>
<th>Type</th>
<th>Magnitude</th>
</tr>
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<tbody>
<tr>
<td>Triazole</td>
<td>-</td>
<td>Yes</td>
<td>Long</td>
<td>AUC/MIC</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Polyene</td>
<td>Yes</td>
<td>-</td>
<td>Long</td>
<td>Peak/MIC</td>
<td></td>
<td>4 (10)</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Yes</td>
<td>Yes</td>
<td>Short</td>
<td>t &gt; MIC</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>Echinocandin</td>
<td>Yes</td>
<td>-</td>
<td>Long</td>
<td>Peak/MIC</td>
<td></td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

AUC area under the curve, Magnitude 0% maximal efficacy in animal models, *maximal efficacy, MIC minimum inhibitory concentration, PAE post-antibiotic effect.
but also by prolonged persistent growth suppression. The prolonged growth suppression or PAE increases the importance of concentration or the total amount of drug administered. The AUC represents the total amount of drug exposure and the AUC/MIC is the predictive pharmacodynamic parameter. Several studies have demonstrated that efficacy with drugs from the triazole class is related to the AUC of exposure [6,24,27•]. For example, multiple-dosing regimen studies with the triazole, ravuconazole, demonstrated that outcome was most strongly related to the 24 h AUC/MIC parameter (Figure 2). Observations with four drugs from the triazole class suggest that the pharmacodynamic parameter associated with efficacy is similar within this drug class as has been described for drugs within various antibacterial classes [6,24,27•].

Figure 1. Pharmacokinetics of antimicrobial dosing relative to organism MIC.

AUC area under the curve, MIC minimum inhibitory concentration. Parameters of interest: %t > MIC, Cmax/MIC ratio, AUC/MIC ratio.

Figure 2. Relationship between total drug ravuconazole pharmacokinetic/pharmacodynamic parameters and efficacy in a murine candidiasis model.
Pharmacodynamic parameter magnitude

Studies demonstrating the importance of a specific pharmacodynamic parameter define whether a drug class is likely to be most efficacious when dosed frequently or infrequently. Additional studies have been undertaken with organisms varying in susceptibility to the drug to help define the amount of drug or pharmacodynamic parameter magnitude necessary for treatment success. The magnitude of the pharmacodynamic parameter or the pharmacodynamic target, defines the parameter value (%t > MIC, 24 h AUC/MIC, or peak/MIC) that has been shown to predict treatment efficacy. These values define the pharmacokinetic parameter (peak level, AUC and amount of time above a concentration) relative to the MIC of the infecting pathogens that is associated with a favorable outcome. Studies have demonstrated that the magnitude of a pharmacodynamic parameter associated with efficacy is similar for drugs within the same class provided that free drug levels are considered [1••]. Furthermore, in extensive studies with antibacterials, this parameter magnitude has been shown to be independent of the animal species, dosing interval, site of infection and most often the infecting pathogen [1••,2]. For example, the time above MIC necessary for R-lactam antibiotic efficacy in a mouse (maintaining serum antibiotic concentrations above the MIC of the organism for 40 to 50% of the dosing interval) is the same as that needed for efficacy in humans (Figure 3). This concordance among species is not surprising if one considers two factors. First, the drug target for an antimicrobial is in the organism and not in the animal and thus does not vary from species to species.

Second, expressing drug dose as a pharmacodynamic parameter magnitude corrects for differences in pharmacokinetics among animal species. Figure 3 demonstrates the strong relationship between R-lactam %t > MIC in both rodent thigh sepsis and pneumonia models against various bacterial pathogens with widely varying MIC values. Importantly, analyses of the relationship between the pharmacokinetics of (3-lactams and treatment efficacy of pneumococcal infections of the upper respiratory tract in humans found that a similar t > MIC magnitude predicted successful treatment outcome (Figure 4) [1••,2,3].

Pharmacodynamics in antibacterial drug development

The predictive value of animal model pharmacodynamic studies has aided several areas of drug development. For the pharmaceutical industry, animal model pharmacodynamics has allowed early comparison of in vivo drug potency. Comparison of drug potency based upon in vitro potency alone can be misleading. For example, in the development of new generation fluoroquinolones (FQs), a compound such as gemifloxacin (LG Chemical Ltd) would appear to represent a significant advance based upon MIC values 10- to 100-fold lower than with other drugs within the class [28]. However, this drug has a remarkably higher degree of protein binding. If one considers drug pharmacokinetics of this and other FQs, including protein binding, the relative change in in vivo potency for this new ‘more potent’ drug is less than in vitro data would predict (Figure 5) [1••,20,21,28].

Figure 3. Relationship between S-lactam and the change in log o CFU/thigh or lung for various pathogens.

| Relationship between the change in log<sub>10</sub> CFU/thigh or lung for various pathogens following 24 h of therapy with different doses of penicillin, cephalosporins and carbapenems. Each symbol represents data for two mice. The dashed horizontal line represents the number of organisms at the start of therapy. CFU colony-forming units, MIC minimum inhibitory concentration. |

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Figure 4. Relationship between %t > MIC of P-lactams and bacteriological eradication of pneumococci in otitis media and sinusitis.

Circles represent data with penicillins, squares represent data with cephalosporins and triangles represent data from sinusitis. MIC minimum inhibitory concentration.


Figure 5. Pharmacokinetics of fluoroquinolones.

The 24 h AUC/MIC associated with the treatment efficacy of one highly protein bound fluoroquinolone, gemifloxacin, compared with two lower bound fluoroquinolones, gatifloxacin and sitafloxacin in a murine infection model. The symbols represent the 24 h AUC/MIC for the quinolone dosing regimen that produced a net bacteriostatic effect in a murine thigh infection model. Unfilled symbols represent free drug (unbound) levels. Filled symbols represent total drug (protein bound) levels [28].

Pharmacodynamic analyses in early drug development has aided the choice of appropriate dosing regimens for clinical trials. Traditionally, the choice of an antimicrobial dosing regimen for clinical trials has been based upon mean pharmacokinetic values from healthy volunteers. The goal of a dosing regimen has been to achieve drug levels exceeding a single MIC value, often the MIC. However, recent studies in patients under therapy with antimicrobials have demonstrated remarkable variation in pharmacokinetics [29].

MIC distributions have led to a method of dosing regimen prediction termed Monte Carlo simulation [4••,30,31]. This methodology utilizes a pharmacodynamic magnitude or target identified through animal model studies. Next, the pharmacokinetic variation is taken into consideration by performing population pharmacokinetics, ideally sampling from a patient population under therapy with the antimicrobial study drug. The intent of the population pharmacokinetic method is to assess the variability of pharmacokinetic parameters and to identify factors that can alter drug concentrations in patients. The second variable considered is the entire MIC distribution. Similarly, the attempt is to consider all MIC values that one might encounter in practice. Large surveillance databases, such as the SENTRY program, often provide the best source for this information. Monte Carlo simulation is a powerful statistical tool that is able to simulate drug exposure and MIC relationships for large numbers of patients (5000 to 10,000) and predict the probability of attaining the pharmacodynamic target. The end result is a power prediction of the likelihood of a dosing regimen providing a desired drug exposure that would cover the range of organism MIC values likely to be encountered. An acceptable probability is then determined (eg, 95% has been used most often).

Studies that define a pharmacodynamic magnitude target for a drug have also been utilized by regulatory agencies such as the National Committee for Clinical Laboratory Standards (NCCLS) and the Food and Drug Administration (FDA) to aid the development of preliminary susceptibility breakpoints for new antimicrobials [5,32]. The NCCLS has formally adopted pharmacodynamic analysis as one of several criteria for the development of in vitro susceptibility breakpoints [5], eg, a pharmacodynamic magnitude target for a specific drug can be extracted from animal model studies. This target is then considered relative to the MIC distribution from large surveillance databases and to the pharmacokinetics of the specific drug in humans.

Pharmacodynamic parameter magnitude: Triazoles

The use of antifungal pharmacodynamics for drug development has been considered [22•,33,34•,35•]. The most complete analyses available thus far are with the triazole drug class. Initial in vivo pharmacodynamic studies with fluconazole demonstrated that a 24 h AUC/MIC magnitude of approximately 25 produced efficacy against *Candida albicans* with widely varying MIC values [6,27•,36-38]. Similar investigations with three triazoles under development demonstrated that a similar pharmacodynamic target was necessary for efficacy in this in vivo model (Figure 6) [22•]. These experiments also demonstrated the importance of including pharmacokinetic variables such as protein binding in analyses, and that the free (unbound) pharmacodynamic magnitude target is most relevant for comparison among drugs. In vivo model pharmacodynamic analysis with triazole compounds has been undertaken with four triazole compounds in two different animal infection model species (mouse and rat), in both compromised and immunocompetent infection models (neutropenic and non-neutropenic). Comparing MIC values...
fold: variation in organism resistance mechanism (efflux pumps and reduced drug target affinity) was observed, and both survival and microbiological endpoints were utilized [6,24,27,36-38]. The 24 h AUC/MIC magnitude necessary for efficacy in these investigations has been independent of these numerous study variables. Thus, similar to studies with antibacterial drugs, the pharmacodynamic parameter magnitude predictive of efficacy is similar within a drug class, among animal species, infection sites, and for organisms with varying in vitro susceptibility. The important areas not yet addressed by these investigations include the impact of additional degrees to which the host is immunocompromised, study of filamentous fungi in these models, and the study of the pharmacodynamics of drugs in combination.

Figure 6. Relationship between pharmacodynamics of triazoles and animal models of candidiasis.

Relationship between the 24 h AUC/MIC for free triazole drug levels, the MIC and efficacy in animal models of candidiasis. The open circles represent the 24 h AUC/MIC value for the dosing regimen that produced study-defined efficacy. The efficacy endpoints in these studies include the dose necessary to produce 50% of maximal microbiological efficacy and the dose associated with 80% survival in infected animals.


Triazole pharmacodynamics in clinical trials

Correlations of human pharmacokinetics and clinical trial outcome with several antibacterial classes have suggested that the pharmacodynamic parameter magnitude, which produces efficacy in animal models, also predicts efficacy in humans. The strength of this relationship has been strongest in the analysis of otitis media and sinusitis where the study endpoint was microbiological eradication (Table 2) [1••,2,3,19•]. Unfortunately, there is no analogous database of antifungal clinical trials and there are a number of barriers to this type of analysis. Most importantly, the successful outcome among patients with fungal infections is often most closely related to the underlying host immunodeficiency predisposing to infection. In addition, the nature of these trials most often precludes determination of proven microbiological eradication. Despite these limitations, there

between drug dose, organism MIC and clinical outcome (Table 2) [39••]. The largest published dataset is with fluconazole in the treatment of mucosal candidiasis. If the data presented in the NCCLS susceptibility guideline publication is examined, the relationship between treatment success and the magnitude of the 24 h fluconazole AUC/MIC is very similar to that observed in animal model pharmacodynamic studies. Importantly, a fluconazole AUC/MIC magnitude of approximately 25 is supportive of the susceptibility breakpoint guidelines suggested in the NCCLS publication. There is an additional small series of patients with candidemia and deep Candida infection that provide information allowing the examination of the relationship between fluconazole AUC/MIC and efficacy against Candida spp [40,41]. In each of these reports the fluconazole 24 h AUC/MIC values predictive of outcome in these systemic Candida infections was similar to values predictive of outcome in mucosal disease. While these small series do support this pharmacodynamic extrapolation to patients with systemic candidiasis, it will be important to confirm this relationship with larger databases. Two factors making the analysis of currently available candidemia datasets difficult include the lack of MIC variation and antifungal dosing that would produce very high 24 h AUC/MIC values. For example, analysis of the relationship between voriconazole pharmacokinetics, organism MIC and efficacy in clinical trials failed to demonstrate a strong correlation between MIC and outcome [D Sheehan, unpublished data]. However, if the 24 h AUC/MIC based on the current clinical dose and MIC,... is considered, the value would far exceed 25. Thus, data from the great majority of patients in these databases lie far to the right (maximal efficacy) in the dose-response curve or relationship. This makes it difficult to determine if treatment success is related to an antifungal treatment regimen or to the underlying host immunodeficiency.

Table 2. Fluconazole pharmacodynamics in clinical trials.

<table>
<thead>
<tr>
<th>MIC</th>
<th>Number of patients</th>
<th>AUC/MIC 24h</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV oropharyngeal candidiasis* [39••]</td>
<td>403</td>
<td>17</td>
<td>92</td>
</tr>
<tr>
<td>≤ 8</td>
<td>16 to 32</td>
<td>15*</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>Non-HIV candidemia* [41]</td>
<td>22</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>≤ 8</td>
<td>6 to 32</td>
<td>8 to 4</td>
<td>7</td>
</tr>
<tr>
<td>64</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Non-HIV candidemia and deep candidiasis] [40]</td>
<td>24</td>
<td>30</td>
<td>79</td>
</tr>
<tr>
<td>≤ 8</td>
<td>16 to 32</td>
<td>15 to 8</td>
<td>67</td>
</tr>
<tr>
<td>≥ 64</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*400 mg/day with MIC 16 μg/ml, 800 mg/day with MIC 32 μg/ml; ≥200 mg/day; *400 mg/day.
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Pharmacodynamic magnitude: Other antifungal drug classes
Parameter magnitude studies with other antifungal drug classes in animal models are less complete. One factor that has limited the study of parameter magnitude predictions with polyene and echinocandin drug classes is the narrow range in MIC values of available pathogens. However, animal model pharmacodynamic studies with these drug classes that have used strains with similar in vitro susceptibility have suggested that maximal efficacy is achieved when peak/MIC values exceed 10 [7,23]. Similar analysis with the antifungal, flucytosine is limited to a study with a single Candida isolate making extrapolation difficult [8]. However, maximal microbiological efficacy was observed with this strain when serum levels exceeded the MIC value for only 25% of the dosing interval.

Pharmacodynamics of other antifungal classes in clinical trials
Unfortunately, there are no clinical trials that have lent themselves to an analysis that would provide an insight to this parameter magnitude question. However, several pharmaceutical companies have begun to consider pharmacodynamic analysis in the development of new compounds.

Future pharmacodynamic analysis in drug development
There remain many important unanswered antifungal pharmacodynamic questions. Will a larger pharmacodynamic parameter magnitude be required to successfully treat infections in patients with varying immunodeficiencies such as neutropenia? Do the pharmacodynamic predictions observed with drugs in relationship to Candida infections predict outcome with filamentous organisms such as Aspergillus? Certainly the high rate of treatment failure observed with this group of organisms suggests that a higher magnitude may be required. Also important for examining the pharmacodynamics in the treatment of filamentous fungal infections will be the examination of the pharmacodynamic relationships of drugs utilized in combination.

Conclusions
Application of pharmacodynamic principles to antifungal drugs has provided an understanding of the relationship between drug dosing and treatment outcomes similar to that observed in antibacterial pharmacodynamics. Initial observations with triazole pharmacodynamics have correlated with clinical trial results and proven useful for validation of in vitro susceptibility breakpoints. There are additional antifungal pharmacodynamic areas under active research, including the pharmacodynamics of antifungals in combination, and antifungal pharmacodynamics in the treatment of other fungal pathogens.

Pharmacokinetic studies have been invaluable for the clinical trial dosing design for numerous antibacterial drugs in the development stage. Similar application to antifungal development should be considered.

References