Clinical pharmacodynamics of antifungals

David Andes, MD

Department of Medicine, Section of Infectious Diseases, University of Wisconsin,
600 Highland Avenue, Room H4/572, Madison, WI 53792, USA

The field of antimicrobial pharmacodynamics examines the relationship between drug pharmacokinetics and antimicrobial efficacy [1]. These studies have been valuable for defining optimal antimicrobial dosing regimens and the development of in vitro susceptibility breakpoints [2-5]. The concepts encompassing this discipline have been defined most thoroughly with antibacterial compounds [1]. With the advent of standardized in vitro susceptibility testing with antifungal compounds, similar pharmacodynamic investigations have been undertaken. Both in vitro and in vivo models have demonstrated a correlation between drug dose, organism minimum inhibitory concentration (MIC), and outcome [6-13]. These investigations have been important for describing the relative potency of antifungal drugs against a number of important pathogens. Recent in vivo pharmacodynamic investigations have examined the relationship among drug dose, dosing interval, MIC, and treatment outcome to define the specific pharmacodynamic parameter and parameter magnitude predictive of antifungal treatment efficacy.

Pharmacodynamic patterns of activity

A variety of in vitro and in vivo studies have examined the impact of antibiotic drug concentration on antimicrobial killing over time or 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 extent and rate antimicrobial activity. When organism reduction is enhanced by increasing drug levels the pattern of activity is referred to as "concentration-dependent." Studies with drugs from the polyene and echinocandin class have demonstrated concentration-dependent killing over a wide range of
parameters is associated with one of the time course of antimicrobial activity patterns described previously (see Table 1). For drugs that demonstrate time-dependent killing and short or no postantibiotic effects, dosing is optimized by prolonging the duration of the drug-organism interaction. The parameter that considers this exposure is the time that drug levels remain above the MIC. Antimicrobials are often administered at lower doses but are dosed more frequently to take advantage of this pattern of activity. Studies examining the pharmacodynamics of flucytosine demonstrated that $T > MIC$ was best predictive of treatment outcome [8]. For drugs exhibiting concentration-dependent killing and long postantibiotic effects, antimicrobial efficacy is optimized with large infrequent doses. The pharmacodynamic parameters that represent this type of dosing strategy include the peak drug level in relation to the MIC and AUC in relation to the MIC. The peak-MIC parameter describes the pharmacodynamic activity of both the polyenes and echinocandins [7,14]. The third pattern of drug activity is characterized by concentration-independent killing but also by prolonged persistent growth suppression, increasing 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 shown that efficacy with drugs from the triazole class is related to the AUC of exposure [6,16,20]. For example, Louie et al [20] demonstrated that outcome with fluconazole against Candida albicans was dependent on the amount of drug or AUC of exposure, but independent of the frequency of dosing (Fig. 2). Observations with four drugs from the triazole class have shown that the 24-hour AUC-MIC parameter is most strongly associated with efficacy, suggesting that the parameter predictive of outcome is similar within the antifungal drug class as has been described for drugs within various antibacterial classes (Fig. 3) [6,16,20].
early drug development has aided in the choice of appropriate dosing regimens for clinical trials. In addition, these analyses have been used in the development of treatment guidelines to optimize dosing with antibiotics already in wide use [23,24]. To define an optimal dosing regimen, first in vivo animal model pharmacodynamic studies are used to define the magnitude of the pharmacodynamic parameter associated with efficacy against organisms with wide variation in MIC, providing a pharmacodynamic target. Next, human pharmacokinetics can then be considered relative to the distribution of MICs for target pathogens and a drug dose chosen to achieve the pharmacodynamic target [4].

Studies that define a pharmacodynamic magnitude target for a drug have also been used by regulatory agencies, such as the National Committee for Clinical Laboratory Standards (NCCLS) and Food and Drug Administration, to aid in developing susceptibility breakpoints for new and already approved antimicrobials [5,25]. Similarly, the pharmacodynamic magnitude target for a drug that has been determined with animal model studies is examined relative to the MIC distribution and to the pharmacokinetics of the drug in humans. More recent use of population pharmacokinetics and stochastic modeling using Monte Carlo simulation has allowed consideration of pharmacokinetic and MIC variation to be included in analyses [4]. This latter powerful analytic method can predict the likelihood that a particular dosing regimen achieves a pharmacodynamic target for a specific MIC. If a dosing regimen is predicted to achieve a pharmacodynamic target
Fig. 4. Relationship between the 24-hour AUC-MIC for free and total triazole drug levels, the MIC, and efficacy in animal models of candidiasis. Efficacy endpoints in these studies include the dose necessary to produce 50% of maximal microbiologic efficacy and the dose associated with 80% survival in infected animals.
treatment of mucosal candidiasis. The largest of these is summarized in the NCCLS antifungal susceptibility breakpoint guideline publication [31]. Data from six fluconazole trials included 460 episodes of oropharyngeal candidiasis in 316 patients with AIDS in which the organism MIC, drug dose, and clinical outcomes were available. One can use the organism MIC and dose in these patients to calculate a 24-hour AUC-MIC value and then examine the relationship between this value and treatment success. When the 24-hour fluconazole AUC-MIC exceeded a value of 25 clinical treatment success was observed in 91% to 100% of patients. When this pharmacodynamic value fell below 25, however, treatment failures were reported in 27% to 35% of cases [32]. The association between the 24-hour AUC-MIC and outcome is very similar to that observed in animal model pharmacodynamic studies. Importantly, the fluconazole AUC-MIC magnitude of near 25 is supportive of the susceptibility breakpoint guidelines suggested in the NCCLS publication. Of additional interest in this publication was the proposal of a new susceptibility category, termed "susceptible-dose dependent," in which the organism is considered susceptible if a higher drug dose is used. In this particular case a fluconazole dose escalation to 400 or 800 mg/d achieves a 24-hour AUC-MIC value around 25 for organisms with MICs up to 16 and 32 mg/L, respectively. There are numerous additional publications of smaller series of patients (range, 2 to 180 patients) with oropharyngeal candidiasis in which treatment failures were associated with an elevated MIC and in which a fluconazole drug dose was provided [33-52]. In toto, data from nearly 1000 patients are available that allow analysis of the relationship among MIC, drug dose, and outcome (see Table 2). For nearly all treatment failures reported, the estimated fluconazole AUC-MIC value would have fallen below a value of 25, again in line with predictions from animal models.

Pharmacodynamic analysis of studies in patients with candidemia and deep Candida infection is more difficult. Most of the larger trials in treatment of candidemia provide few data with organisms for which the MIC is elevated. It is difficult to show a relationship between MIC and outcome because the AUC-MIC values are above a value at which one expects failures related to drug therapy. For example, in the large candidemia trial examining the efficacy of fluconazole and amphotericin B, among the C. albicans isolates from patients treated with fluconazole the MIC$_{90}$ was 1 mg/L, where the 24-hour AUC-MIC value is eightfold higher than that expected to be associated with treatment failure [53]. In addition, outcome in candidemia can be impacted not only by antifungal therapy and underlying host immune state, but also by management of intravascular catheters, adding yet another potential confounding variable. The NCCLS guideline publication data, however, did include 97 patients with candidemia [31]. It is stated that the relationship between MIC and outcome was similar to that for the patients with mucosal disease. The data for patients with candidemia were not presented separately. There are,
isolate making extrapolation difficult [8]. In study with this strain, however, maximal microbiologic efficacy was observed when serum levels exceeded the MIC for only 25% of the dosing interval.

**Clinical pharmacodynamics of other antifungal drugs**

Unfortunately, there are no clinical trials that have lent themselves to an analysis that provides insight to this parameter magnitude question for other antifungal drug classes. It is hoped that studies with several of the new *Streptococcus pneumoniae* application to breakpoint determinations. Antimicrob Agents Chemother 1998;42:2375-9.


