



Appropriate use of Antimicrobial Agents : PK/PD Approach

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Pharmacokinetics is concerned with the time course of antimicrobial concentrations in serum and body fluids. Pharmacodynamics is concerned with the relationship between those concentrations and the antimicrobial effect. The minimum inhibitory concentration (MIC) is a good indicator of the potency of an antibiotic but indicates nothing about the time course of antimicrobial activity. Parameters such as rate of killing with increasing concentrations and persistent effects (eg, postantibiotic effect and postantibiotic sub-MIC effect) are much better predictors of the time course of antimicrobial activity. These two factors enable one to divide antimicrobials into three major patterns of activity as shown in the table below.

Three patterns of antimicrobial activity.

Pattern of Activity	Antimicrobials	Goal of Therapy and PK/PD Parameter Correlating with Efficacy
Concentration-dependent killing and prolonged persistent effects	Aminoglycosides, fluoroquinolones, daptomycin, ketolides	Maximize concentrations; 24-hr AUC/MIC and peak/MIC
Time-depedent killing and minimal or no persistent effects	Penicillin, cephalosporins, carbapenems, aztreonam	Maximize duration of exposure; T>MIC
Time-dependent killing and moderate to prolonged persistent effects	Macrolides, azithromycin, clindamycin, streptogramins, tetracyclines, glycopeptides, oxazolidinones	Maximize amount of drug; 24-hr AUC/MIC

Specific pharmacokinetic/pharmacodynamic (PK/PD) parameters (eg, peak/MIC ratio, 24-hour AUC/MIC ratio or time above MIC [T>MIC]) are major predictors of the in vivo activity of antibiotics, both in animals and in humans. These parameters are highly interrelated and one needs to compare activity at various doses and dosing frequencies to reduce the interrelationships and determine which PK/PD parameter is most predictive of therapeutic outcome. Multiple dosing regimens are rarely used in human clinical trials, so it is not surprising that all of the PK/PD parameters have been correlated with efficacy in different clinical trials. Much of modern day phar-

macodynamics is in identifying the PK/PD target and the magnitude of the target required for optimal efficacy.

Time above MIC is the primary parameter correlating with the efficacy of β -lactams in animal-infection models. Levels need to exceed the MIC for 40% to 50% of the dosing interval to obtain near maximal activity in these models. Similar T>MICs are required for at least 90% bacteriologic cure in acute otitis media (AOM) and acute maxillary sinusitis. Several studies suggest that similar T>MICs are required in community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae*. The implications of these observations for susceptibility breakpoints, drug-resistant *S. pneumoniae* and for dosing regimens will be discussed. Prolonging the T>MIC can optimize therapy with β -lactams. This has led to longer intermittent infusions or even continuous infusion for some these drugs.

The 24-hour AUC/MIC ratio is the primary parameter for the macrolides, azithromycin, tetracyclines, clindamycin, glycopeptides and oxazolidinones. These drugs lack concentration-dependent killing but differ from the β -lactams in producing prolonged persistent effects. Correlation of results obtained in animal models with clinical outcomes in human infections is not as well established for these drugs.

The 24-hour AUC/MIC ratio and the peak/MIC ratio are primary predictors of the efficacy of fluoroquinolones and aminoglycosides. Peak/MIC levels of 8 to 10 are required for high-response rates with aminoglycosides, which has led to once-daily dosing of these drugs. This form of dosing can also lessen the frequency or the rate at which nephrotoxicity develops. Twenty-four-hour AUC/MIC values of 100 to 125 are associated with high efficacy rates for fluoroquinolones with gram-negative bacilli. Somewhat lower values (around 30-35) are required for efficacy of fluoroquinolones against the pneumococcus. Several of the newer respiratory fluoroquinolones easily reach this goal for most strains of *S. pneumoniae*. Levofloxacin dosing at 500 mg daily provides a more borderline 24-hr AUC/MIC ratio than moxifloxacin and gatifloxacin.

There are a variety of factors that can affect the magnitude of the PK/PD parameter determining efficacy (eg, protein binding). While the magnitude of the PK/PD parameter can vary markedly for different drugs within the same class when total drug is used, the variation is very small when free-drug levels are used to calculate the PK/PD parameter. Dosing frequency and site of infection do not appear to have a major effect on the PK/PD target. There are some variations with different organisms. As stated above, a smaller 24-hour AUC/MIC ratio is required for pneumococci compared with GNB. Staphylococci require a shorter T>MIC for efficacy with beta-lactams than pneumococci and GNB because they are the only organisms in which we have observed in vivo persistent effects. However, the magnitude of the PK/PD parameter remains relatively constant as the MIC increases in more resistant strains. This observation is especially useful for predicting activity of drugs against resistant strains for which there is not sufficient clinical data.

Such data is also helpful in setting clinical or pharmacodynamic breakpoints for antimicrobial susceptibility tests. Pharmacodynamics has become a major factor used by the NCCLS to establish susceptibility breakpoints. Several of the breakpoints for beta-lactams with streptococci have been altered largely because of pharmacodynamics.

Pharmacokinetic/pharmacodynamic parameters also can play a role in preventing the emergence of resistance

during therapy. For example, a 24-hour AUC/MIC value of ≥ 100 is associated with much less resistance than values < 100 with monotherapy with fluoroquinolones. Combination therapy was associated with an even lower value. A variety of experimental studies are being done to better define the role of PK/PD in reducing the selection of resistant organisms.

Pharmacodynamics continues to provide a rationale for optimizing antimicrobial therapy and better defining antimicrobial resistance.