Pharmacodynamic principles can be used to divide antibiotics into two major classes based on their mechanism of bactericidal action: (1) concentration-dependent drugs, such as aminoglycosides and fluoroquinolones, and (2) concentration-independent drugs, including the β-lactams. Antibiotics also differ in the postantibiotic effect (PAE) that they exert. In general, concentration-dependent drugs have a more prolonged PAE than concentration-independent drugs, particularly against Gram-negative pathogens. Pharmacodynamic classifications have important implications for the planning of drug regimens. For concentration-dependent drugs, peak concentration to minimal inhibitory concentration (MIC) ratios of approximately 10 are associated with clinical success. Therefore, high drug levels should be the goal of therapy. This is best achieved by high doses taken once daily. This approach, however, is not feasible for the fluoroquinolones owing to dose-limiting CNS toxicity. Concentration-independent agents are most effective when the duration of serum concentrations is higher than the pathogen’s MIC (time > MIC) for a significant proportion of the dosing interval. Frequent dosing or continuous infusions can increase the time > MIC. Concentrations of antibiotics that are sublethal can permit the emergence of resistant pathogens. Optimization of antibiotic regimens on the basis of pharmacodynamic principles could thus significantly diminish the emergence of antibiotic resistance. (CHEST 1999; 115:19S–23S)

Key words: antibiotic pharmacodynamics; antibiotic pharmacokinetics; concentration-dependent drugs; concentration-independent drugs; continuous infusion; postantibiotic effect

Abbreviations: AUC = area under the time-concentration curve; AUIC = area under the inhibitory curve; MIC = minimal inhibitory concentration; PAE = postantibiotic effect

Many factors can contribute to the development of bacterial resistance to anti-infective agents, but one of the most important risk factors is repeated exposure to suboptimal antibiotic concentrations. Pharmacodynamic data, which describe the relationship between drug serum concentration and the pharmacologic effects of the drug, may be useful in designing regimens that minimize the likelihood of exposing pathogens to sublethal drug levels. This article will review some of the key principles of antibiotic pharmacodynamics and discuss the implications of these data for improving antibiotic regimens and preventing the emergence of resistant pathogens.

Clinical Pharmacology of Antimicrobial Therapy

As shown in Figure 1, pharmacokinetics and pharmacodynamics are interrelated. The pharmacokinetic properties of a drug characterize the rise and fall of drug concentrations in serum or tissue over time. Pharmacodynamic parameters integrate the microbiological activity and pharmacokinetics of an anti-infective drug by focusing on its biological effects, in particular growth inhibition and killing of pathogens.

On the basis of pharmacodynamic properties, antimicrobial agents can be divided into two major groups (Table 1). The first group, which includes the fluoroquinolones and the aminoglycosides, consists of agents that exhibit concentration-dependent killing of pathogens. For this group, the higher the drug concentration, the faster the eradication of pathogens. In the second group, which includes the β-lactam antibiotics, peak concentrations are relatively unimportant. Instead, the length of time that...
concentrations are maintained above the pathogen’s minimal inhibitory concentration (MIC) is critical to bacterial eradication. Members of this group are referred to as concentration-independent or time-dependent drugs.

**Postantibiotic Effect**

The postantibiotic effect (PAE) is the phenomenon of continued suppression of bacterial growth after a short exposure of bacteria to antimicrobial agents. This effect is probably the result of several mechanisms, including nonlethal damage caused by the antibiotic and continued persistence of the drug at the bacteria’s drug-binding site for a time after the antibiotic and continued persistence of the drug is removed.

The PAE is influenced by several factors, including the microorganism, the inoculum size, the antibiotic, the concentration of antibiotic, and the duration of exposure. Distinctions in PAE between Gram-positive and Gram-negative pathogens have also been observed. For many antibiotics, including β-lactam agents, the PAE against Gram-positive pathogens lasts approximately 1 to 2 h. Aminoglycosides and fluoroquinolones also demonstrate a Gram-negative PAE of about ≤ 2 h. However, β-lactam drugs other than imipenem show a negligible PAE against Gram-negative bacteria. Accordingly, once concentrations of these drugs fall below the MIC, beneficial antibiotic effects disappear and Gram-negative pathogens can start reproducing.

PAEs determined by *in vitro* methods may not always reflect *in vivo* PAE. However, *in vitro* PAEs often underestimate the duration of the PAE observed *in vivo*. Exceptions to this, however, are PAEs for streptococci that have been exposed to penicillins or cephalosporins. In this system, penicillins exhibit significant PAEs against streptococci *in vitro* but no PAEs *in vivo*. PAEs measured *in vitro* may also incorrectly predict the effect of multiple dosing. *In vitro*, the PAE of aminoglycosides is lost after multiple dosing, while *in vivo* PAEs appear to continue.

**The Correlation Between Pharmacodynamic Parameters and Clinical Success**

The pharmacodynamic parameters that correlate with clinical success differ for concentration-dependent drugs vs those that are relatively concentration independent (Table 1). For the concentration-dependent drugs (aminoglycosides, fluoroquinolones), the best predictive parameter is either the ratio of peak drug concentration to MIC or the ratio of area under the concentration curve (AUC) to MIC. In a study of the clinical response to aminoglycosides, a highly significant difference (p = 0.00001) was found in the ratio of maximal peak drug concentrations to MIC between patients who did not respond to therapy and those who did. Further analyses indicated that as the maximal peak to MIC ratios increased, so did the clinical response rate. An approximately 90% response rate was achieved at ratios of 8 to 12 (Fig 2).

These data indicate that for aminoglycosides, maximum drug concentrations of at least 10 to 12 times the MIC are needed for the successful treatment of pathogens. Similar results have been demonstrated for the fluoroquinolones in a neutropenic model of Pseudomonas sepsis. However, toxic side effects associated with the fluoroquinolones prevent the attainment of high peak concentrations in clinical settings. For this reason, many studies have examined AUC to MIC ratios instead; this parameter is also referred to as area under the inhibitory curve (AUIC). Increasing AUICs have been correlated with a higher level of clinical and microbiological cures in patients with pneumonia treated with ciprofloxacin. The critical AUIC ratio needed for success in this case appears to be approximately 125 times the MIC. AUIC values lower than this are associated with microbiological cure rates of < 30%, while AUIC values above this result in microbiological cure rates of > 80%. The AUICs of a particular drug can vary widely. For example, the MIC of *Pseudomonas aeruginosa* to trovafloxacin is 1 μg/mL. Hence, the AUIC for 200 mg po qd and 300 mg IV qd would be 34 and 46, respectively.

For concentration-independent drugs such as the β-lactams, the key parameter associated with clinical success is the percent of time that drug levels at the site of infection exceed the MIC (time > MIC). Percent of time above MIC of > 40% generally correlates with high bacteriologic cure rates (Fig 3). The time above the MIC required for maximal β-lactam activity may differ depending on the pathogen. In animal studies, the maximal effect of β-lactams against *Staphylococcus aureus* is observed when the time above the MIC is greater than
approximately 40% of the dosing interval. For *S. pneumoniae* and Enterobacteriaceae, maximal effect is seen when 60 to 70% of the dosing interval is above the MIC.\textsuperscript{12} For example, the MIC\textsubscript{50} of *P. aeruginosa* to piperacillin/tazobactam is 8.0 \(\mu\)g/mL.\textsuperscript{11} Hence, the time above the MIC for piperacillin/tazobactam, 3.375 g IV q4h, would be the entire dosing interval. Even if the MIC\textsubscript{90}, a more conservative value, were utilized, the time above the MIC would still be 50%.

Alternatively, clinical response to the \(\beta\)-lactams has been shown to correlate with AUIC; this is not surprising, as an increase in the AUIC would also result in increased time above the MIC. Because of its relevance to both concentration-dependent and concentration-independent drugs, the AUIC has been proposed as a universal pharmacodynamic parameter for assessing the clinical efficacy of all anti-infective agents. However, \(\beta\)-lactam antibacterial activity more closely correlates with time above the MIC than with AUIC.\textsuperscript{12}

### Optimizing Antibiotic Regimens on the Basis of Pharmacodynamic Characteristics

An understanding of the pharmacodynamic characteristics of an antibiotic can provide insights into the best regimen for a given drug. For concentration-dependent antibiotics, a high once-daily dose is the best way to eradicate pathogens. This approach has been successful for aminoglycosides but cannot be applied to fluoroquinolones because CNS toxicity may result from high doses. Possible ways to optimize fluoroquinolone regimens include the administration of larger doses than conventionally used or the addition of a second agent to the regimen.\textsuperscript{13}

For concentration-independent drugs, the goal is to maximize the time that drug levels at the site of infection exceed the pathogen's MIC. One way of achieving this is through continuous infusions, which provides a prolonged time > MIC compared with bolus dosing.\textsuperscript{13} The enhanced duration of the antibiotic effect may be particularly important in immunosuppressed patients or in the treatment of pathogens with high MICs. Continuous infusions also reduce the amount of drug required for treatment.

Continuous infusions of ceftazidime have been

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**Table 1—Summary of Pharmacodynamic Characteristics of Antimicrobial Agents**

<table>
<thead>
<tr>
<th>Pharmacodynamic Characteristic</th>
<th>Representative Antimicrobial Agents</th>
<th>Goal of Regimen</th>
<th>Parameters Correlating With Clinical Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration-dependent killing</td>
<td>Aminoglycosides, fluoroquinolones, metronidazole</td>
<td>Maximize concentrations</td>
<td>Ratio of maximum peak concentration to MIC; ratio of AUC to MIC</td>
</tr>
<tr>
<td>Concentration-independent killing</td>
<td>Penicillins, cephalosporins, aztreonam</td>
<td>Maximize exposure time</td>
<td>Time above MIC levels</td>
</tr>
</tbody>
</table>

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**Figure 2.** Relationship between the maximal peak plasma level to MIC ratio and the rate of clinical response in 236 patients with Gram-negative bacterial infection treated with aminoglycosides (gentamicin, tobramycin, or amikacin). Vertical bars represent SE values. From Moore et al,\textsuperscript{9} with permission.

**Figure 3.** Pharmacodynamics of \(\beta\)-lactams: the relationship between the time above MIC against *S. pneumoniae* (open symbols) and *Haemophilus influenzae* (closed symbols) and bacteriologic cure. From Craig and Andes,\textsuperscript{18} with permission.
thoughtful attention to dosing. In 12 volunteers, continuous infusion regimens appeared to have advantages over standard intermittent bolus dosing, particularly with respect to time > MIC (Table 2). In addition, continuous infusion allowed a reduction in total daily dose compared with conventional regimens. No adverse effects were observed in healthy volunteers or critically ill patients receiving continuous infusions of ceftazidime.

Although initial results with continuous infusion regimens are promising, several issues need to be addressed, including the tissue concentrations achieved, adverse reactions, drug stability and compatibility, and ideal concentration/MIC ratio. Perhaps the most important issue, however, is efficacy. Although pharmacokinetic data indicate that continuous infusion of β-lactam agents should be clinically effective, to my knowledge, efficacy has not been addressed by the studies conducted to date.

**IMPLICATIONS FOR DRUG RESISTANCE**

The presence of sublethal concentrations of a drug exerts selective pressure on a population of pathogens without eradicating it. Under these circumstances, mutant strains that possess a degree of drug resistance are favored and tend to dominate the population. From such populations with low-level resistance, more highly resistant organisms are more readily selected. It thus follows that one tactic to prevent the emergence of resistance is to minimize the time that suboptimal drug levels are present by thoughtful attention to dosing.

For fluoroquinolones and aminoglycosides, optimal dosing means maintaining high maximum peak concentration to MIC ratios. Pharmacodynamic data thus predict that problems with resistance may arise when fluoroquinolones are used to treat pathogens with high MIC values, such as Pseudomonas, because the highest drug levels attained are only approximately four to five times the MIC; the optimal level would be 10 times the MIC. Similarly, AUIC < 125 times the MIC indicates suboptimal dosing.

For β-lactam agents, increasing the duration of time above the MIC should help prevent the emergence of resistance. For drugs with relatively short half-lives, levels four to five times the MIC can be maintained over extended intervals by more frequent dosing or by continuous infusions.

These predictions are currently theoretical. They are only beginning to be tested in clinical settings. If they are confirmed, however, it will suggest that clinicians need to consider pharmacodynamic properties when choosing an antibiotic therapy. Choosing a drug with the appropriate spectrum of activity will always remain important in treating bacterial infections. However, choosing the right dose and dosing interval may also be critical to achieving optimal clinical responses and preventing the emergence of resistant pathogens.

**APPENDIX/DISCUSSION**

**Dr. Burgess:** The MIC I am quoting here is for the specific pathogen causing the infection—so it is the actual MIC, not the MIC50 or MIC90. When considering pharmacodynamic relationships, people refer to the MIC50 or the MIC90, but those are for groups of organisms. Some people have tried to use the MIC50 to define dosing regimens, but that is not conservative enough since only half of your Staphylococcus, *Escherichia coli,* or other pathogenic isolates are being inhibited. We should be using the MIC90 to be more conservative, although we are probably then overdosing from an empiric standpoint. Once you get the data back from the clinical microbiology laboratory, you will have the specific MIC, which you can then use for determining dosage.

**Dr. Rapp:** We know that with aminoglycosides we can minimize the effects on human cells by having drug-free intervals. What kind of side effects are we having on mammalian cells with these other drugs during continuous infusion?

**Dr. Burgess:** We really do not know. We do know that with continuous infusion of ceftazidime, we can use less drug and maintain the dynamics a lot better—for example, staying at four times the MIC. But with regard to the adverse reaction profile for continuous infusion in the clinic, we do not have enough data.

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**Table 2—Effect of Dosing Regimen on the Percentage of Dosing Interval in Which Ceftazidime Serum Concentrations Exceed the MIC in 12 Healthy Volunteers**

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>For Organisms Whose MIC = 4 mg/mL</th>
<th>For Organisms Whose MIC = 8 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g q12h</td>
<td>52</td>
<td>37</td>
</tr>
<tr>
<td>1 g q8h</td>
<td>82</td>
<td>61</td>
</tr>
<tr>
<td>2 g CI/24 h</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3 g CI/24 h</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*CI = continuous infusion. Adapted from Nicolau et al., with permission.*
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