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A PK/PD APPROACH TO ANTIBIOTIC THERAPY

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Introduction

Pharmacokinetics (PK) is concerned with the time course of antimicrobial concentrations in the body, while pharmacodynamics (PD) is concerned with the relationship between those concentrations and the antimicrobial effect. Antibiotic dosing regimens have traditionally been determined by PK parameters only. However, PD plays an equal, if not more important, role. In this age of increasing antimicrobial resistance, PD becomes even more important because these parameters may be used to design dosing regimens which counteract or prevent resistance.

Discussion

The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro. While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity.

PK parameters quantify the serum level time course of an antibiotic. The three pharmacokinetic parameters that are most important for evaluating antibiotic efficacy are the peak serum level (Cmax), the trough level (Cmin), and the Area Under the serum concentration time Curve (AUC). While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic.

Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic: the Peak/MIC ratio, the T>MIC, and the 24h-AUC/MIC ratio. The Peak/MIC ratio is simply the Cpmax divided by the MIC. The T>MIC (time above MIC) is the percentage of a dosage interval in which the serum level exceeds the MIC. The 24h-AUC/MIC ratio is determined by dividing the 24-hour-AUC by the MIC.
Antimicrobial Patterns

The three pharmacodynamic properties of antibiotics that best describe killing activity are time-dependence, concentration-dependence, and persistent effects. The rate of killing is determined by either the length of time necessary to kill (time-dependent), or the effect of increasing concentrations (concentration-dependent). Persistent effects include the Post-Antibiotic Effect (PAE). PAE is the persistent suppression of bacterial growth following antibiotic exposure.

Using these parameters, antibiotics can be divided into 3 categories:

<table>
<thead>
<tr>
<th>Pattern of Activity</th>
<th>Antibiotics</th>
<th>Goal of Therapy</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong>&lt;br&gt;Concentration-dependent killing and Prolonged persistent effects</td>
<td>Aminoglycosides, Daptomycin, Fluoroquinolones, Ketolides</td>
<td>Maximize concentrations</td>
<td>24h-AUC/MIC, Peak/MIC</td>
</tr>
<tr>
<td><strong>Type II</strong>&lt;br&gt;Time-dependent killing and Minimal persistent effects</td>
<td>Carbapenems, Cephalosporins, Erythromycin, Linezolid, Penicillins</td>
<td>Maximize duration of exposure</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td><strong>Type III</strong>&lt;br&gt;Time-dependent killing and Moderate to prolonged persistent effects</td>
<td>Azithromycin, Clindamycin, Oxazolidinones, Tetracyclines, Vancomycin</td>
<td>Maximize amount of drug</td>
<td>24h-AUC/MIC</td>
</tr>
</tbody>
</table>

For **Type I** antibiotics (AG’s, fluoroquinolones, daptomycin and the ketolides), the ideal dosing regimen would maximize concentration, because the higher the **concentration**, the more extensive and the faster is the degree of killing. Therefore, the 24h-AUC/MIC ratio, and the Peak/MIC ratio are important predictors of antibiotic efficacy. For aminoglycosides, it is best to have a Peak/MIC ratio of at least 8-10 to prevent resistance.
For fluoroquinolones vs gram negative bacteria, the optimal 24h-AUC/MIC ratio is approximately 125. Versus gram positives, 40 appears to be optimal. However, the ideal 24h-AUC/MIC ratio for FQ’s varies widely in the literature.

**Type II** antibiotics (beta-lactams, clindamycin, erythromycin, and linezolid) demonstrate the complete opposite properties. The ideal dosing regimen for these antibiotics maximizes the **duration** of exposure. The T>MIC is the parameter that best correlates with efficacy. For beta-lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval.

**Type III** antibiotics (vancomycin, tetracyclines, azithromycin, and the dalfopristin-quinupristin combination) have mixed properties, they have time-dependent killing and moderate persistent effects. The ideal dosing regimen for these antibiotics maximizes the **amount** of drug received. Therefore, the 24h-AUC/MIC ratio is the parameter that correlates with efficacy. For vancomycin, a 24h-AUC/MIC ratio of at least 125 is necessary (some researchers recommend a ratio of 400 or more for problem bugs).

**Outcome studies**

**Aminoglycoside Pharmacodynamics in Vivo**

<table>
<thead>
<tr>
<th>Initial serum peak level</th>
<th>Died</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5mcg/ml</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td>&gt;= 5mcg/ml</td>
<td>2%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Moore et al, J Infect Dis 149: 443, 1984
Aminoglycoside Pharmacodynamics in vivo

![Graph showing response rate vs peak/MIC ratio](image)

Moore et al, J Infect Dis 155: 93, 1987

Vancomycin Outcome vs 24h-AUC/MIC ratio

<table>
<thead>
<tr>
<th>24h-AUC/MIC ratio</th>
<th>Satisfactory</th>
<th>Unsatisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 125</td>
<td>4 (50%)</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 125</td>
<td>71 (97%)</td>
<td>2</td>
</tr>
</tbody>
</table>


Fluoroquinolone Pharmacodynamics vs S. pneumoniae

<table>
<thead>
<tr>
<th>24h-AUC/MIC ratio</th>
<th>Microbiological Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 33.7</td>
<td>(64%)</td>
</tr>
<tr>
<td>&gt; 33.7</td>
<td>(100%)</td>
</tr>
</tbody>
</table>


Pharmacodynamics of Beta-Lactams and Macrolides in Otitis Media

![Graph showing bacteriologic cure vs time > MIC](image)

Craig et al, Ped Infect Dis 15: 255, 1996
Conclusion

PK dosing has shown us that one dose is not appropriate for all patients. Pharmacodynamics shows us that one target level is not appropriate for all patients. We need to evaluate both the serum level data and the MIC, taking into consideration the PD properties of the drug.

Numerous outcome studies have shown that class-appropriate PK/PD parameters are excellent predictors of antibiotic efficacy.

References