Re-evaluating current antibiotic therapy

W. A. CRAIG

William S. Middleton Memorial VA Hospital, Madison, Wisconsin, U.S.A.

Pharmacokinetic/pharmacodynamic (PK/PD) parameters derived from animal and clinical models of infection are used to predict bacteriological efficacy. Growing evidence from the clinical setting supports the validity of these parameters in guiding antimicrobial therapy. For example, in otitis media and sinusitis, high bacteriological cure rates are obtained when serum concentrations of β-lactams and macrolides exceed the MIC of the infecting pathogen for at least 40% of the dosing interval. Likewise, the 24-hour AUC/MIC ratio is a good predictor of both bacteriological and clinical efficacy for azithromycin in otitis media and fluoroquinolones in bacterial pneumonia.

The value of PK/PD relationships has been recognized by the National Committee for Clinical Laboratory Standards (NCCLS) as another important factor to consider when establishing susceptibility breakpoints. Recent changes to NCCLS breakpoints for oral β-lactams for Streptococcus pneumoniae reflect this. Also, PK/PD parameters may play a role in predicting the impact of an antibiotic on the development and spread of resistant organisms. In an era of increasing resistance, we should select agents and doses that provide drug concentrations that exceed the magnitude of the PK/PD parameter required both for efficacy and to combat the emergence and spread of bacterial resistance.

Key words: bacteriological eradication; nasopharyngeal carriage; pharmacodynamics; pharmacokinetics; pneumococcal resistance; susceptibility breakpoints.

Introduction

Increasing antimicrobial resistance among common respiratory pathogens (e.g. Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) has the potential to reduce the efficacy of many oral drugs commonly used to treat respiratory infections (see Garau, "Clinical failures: the tip of the iceberg?", this issue) with patient and societal consequences. Thus, there is a need for a move towards preferentially using only those agents with sufficient potency and pharmacokinetic characteristics that will provide clinical activity against sensitive and resistant bacterial pathogens. In concert with this, measures to control colonization and infection with resistant organisms should also be undertaken.

The goal of antimicrobial therapy is to maximize bacterial killing—simply inhibiting the pathogen may allow persistent colonization, recurrence of infection or permit the spread of resistant pathogens between individuals (1). The pharmacology of antimicrobial therapy can be divided into two distinct components—pharmacokinetics (PK) and pharmacodynamics (PD). PK refers to the absorption, distribution and elimination of drugs. These factors, combined with the dose regimen, determine the time course of antibiotic concentrations in serum which, in turn, influence the time course of antibiotic concentrations in tissue and body fluids. The time course of drug concentrations at the site of infection is of key interest with respect to antimicrobial treatment. On the other hand, PD describes the relationship between serum concentrations and drug pharmacology and toxicology. For antimicrobial therapy, the relationship between concentration and antimicrobial effect is crucial (2). The inter-relationship between PK and PD determines the dosing duration and total dose required for optimal antimicrobial activity.

This report offers an overview of the inter-relationship between PK/PD and efficacy for the various antimicrobial agents used for the treatment of RTIs. The value of PK/PD parameters in predicting the impact of antibiotic dose regimens on the selection of antibiotic resistance or maintenance of resistant clones is also examined.

Nature of PK/PD parameters for common antibiotics

Over the past decade, a number of studies have evaluated the predictive nature of PK/PD parameters with regard to in vivo bacteriological eradication. Specific PK/PD parameters (e.g. peak1/MIC, AUC2/MIC ratio and time above MIC) have all been shown to be major determinants of

1Peak plasma concentration
2Area under the serum concentration versus time curve
**Table 1. PK/PD parameters predictive of bacteriological efficacy**

<table>
<thead>
<tr>
<th>Antimicrobial effect</th>
<th>PK/PD parameter</th>
<th>Antimicrobial class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration-dependent killing and prolonged persistent effects</td>
<td>AUC/MIC or peak/MIC</td>
<td>Fluoroquinolones, aminoglycosides, ketolides</td>
</tr>
<tr>
<td>Time-dependent killing and minimal–moderate persistent effects</td>
<td>Time of dosing interval above MIC</td>
<td>Carabapenems, cephalosporins, clindamycin, macrolides, monobactams, oxazolidinones, penicillins</td>
</tr>
<tr>
<td>AUC/MIC</td>
<td></td>
<td>Azithromycin, streptogramins, tetracyclines, vancomycin</td>
</tr>
</tbody>
</table>

*in vivo* antimicrobial activity. The specific PK/PD parameter correlating with efficacy is largely dependent on whether bacterial killing is concentration or time dependent, and on whether there are prolonged, persistent effects (Table 1). These prolonged persistent effects are known as the post-antibiotic effect (PAE) and the post-antibiotic sub-MIC effect and result in the persistent suppression of bacterial growth following exposure to an antimicrobial agent.

For β-lactams, macrolides and clindamycin, the duration of time that serum concentrations exceed the MIC (time above MIC) provides the most accurate prediction of bacteriological efficacy. In contrast, for drugs such as fluoroquinolones and azithromycin, the AUC/MIC ratio is most important. Thus, even if a fluoroquinolone and a β-lactam had the same *in vitro* activity for a given pathogen, there would be marked differences in the PD that would be important in determining the optimal dose regimen (1).

**Magnitude of PK/PD parameters governing antimicrobial efficacy**

### β-LACTAMS

As β-lactams have a kill rate that is independent of concentration, concentrations higher than the MIC or MBC do not greatly increase bacterial kill. Thus, the dosing regimens should maximize the duration of time that serum drug levels exceed the MIC (time above MIC) provides the most accurate prediction of bacteriological efficacy. In contrast, for drugs such as fluoroquinolones and azithromycin, the AUC/MIC ratio is most important. Thus, even if a fluoroquinolone and a β-lactam had the same *in vitro* activity for a given pathogen, there would be marked differences in the PD that would be important in determining the optimal dose regimen (1).

For β-lactams, macrolides and clindamycin, the duration of time that serum concentrations exceed the MIC (time above MIC) provides the most accurate prediction of bacteriological efficacy. In contrast, for drugs such as fluoroquinolones and azithromycin, the AUC/MIC ratio is most important. Thus, even if a fluoroquinolone and a β-lactam had the same *in vitro* activity for a given pathogen, there would be marked differences in the PD that would be important in determining the optimal dose regimen (1).

**β-LACTAMS**

As β-lactams have a kill rate that is independent of concentration, concentrations higher than the MIC or MBC do not greatly increase bacterial kill. Thus, the dosing regimens should maximize the duration of time that serum drug levels exceed the MIC (2,3). Studies performed in murine models of *S. pneumoniae* thigh and pneumonia infections, using amoxicillin + clavulanate, have shown that bactericidal activity occurs once the duration of time starts to exceed 40% above the MIC in a 24- or 48-hour period (Fig. 1) (4,5). This requirement is independent of the infecting pathogen and its resistance profile.

The double tympanocentesis method has been a useful tool in investigating the clinical relevance of PK/PD parameters for otitis media. In this method, a sample of middle ear fluid is taken just prior to antimicrobial therapy and then again 4–6 days after therapy has commenced and during follow-up when a clinical relapse occurs. This technique allows the bacteriological efficacy of antimicrobials to be directly measured and compared. As a result, much of the clinical data that are available supporting the validity of PK/PD parameters comes from studies in acute otitis media. Some data are also available from studies in sinusitis. Here, a sample of sinus fluid is taken prior to antibiotic therapy and then again about 7–10 days after the start of therapy.

Using data from studies in both otitis media and sinusitis, time above MIC for each of the dose regimens was calculated from mean serum concentrations and the MICs for different organisms were taken from the literature. Figure 2 illustrates the relationship between the time above MIC and bacteriological cure for many β-lactam agents in these two infections. High rates of bacteriological cure (> 80%) were achieved once the time above MIC exceeded 40%. Most of the *S. pneumoniae* isolates were penicillin susceptible, hence the high bacteriological cure rate, which approaches 100% (6). Interestingly, the effect of time above MIC on bacteriological efficacy was independent of infection, which further
supports the general utility of PK/PD parameters in predicting bacteriological efficacy.

Assuming that a time above MIC of at least 40% is required for optimal bacteriological efficacy, then the effect of increased MICs due to antimicrobial resistance can be predicted (Table 2). Most of the currently available β-lactam antimicrobial agents provide adequate times above the MIC for bactericidal activity against penicillin-susceptible strains of S. pneumoniae. However, against penicillin-intermediate S. pneumoniae, only amoxicillin-clavulanate (875 mg/125 mg b.d. or 500 mg/125 mg t.d.), cefuroxime (500 mg b.d.) and ceftriaxone (1 g o.d.) exceed the MIC for at least 40% of the dosing interval (Table 2). Notably, cefaclor (500 mg t.d.) and cefixime (400 mg o.d.) do not exceed the MIC for the entire dosing interval and would, therefore, be ineffective against as many as 90% of these pathogens. Against penicillin-resistant S. pneumoniae, only ceftriaxone would be predicted to be effective against most strains based on time above MIC data and amoxicillin-clavulanate would be the only oral β-lactam providing coverage against a significant proportion of these strains, the other oral β-lactams being largely ineffective (i.e. time > MIC90 = 0). These predictions are supported by clinical data in otitis media. For example, in a study by Dagan et al., bacteriological efficacy with cefaclor (40 mg kg\(^{-1}\) day\(^{-1}\)) in cases due to penicillin-susceptible S. pneumoniae was 81% compared with 100% for amoxicillin (49.5 mg kg\(^{-1}\) day\(^{-1}\)). However, in those patients infected with penicillin non-susceptible S. pneumoniae, bacteriological efficacy with cefaclor was only 35%, but was still as high as 71% for amoxicillin against these strains (7). Similarly, in a separate study with amoxicillin/clavulanate (45/6.4 mg kg\(^{-1}\) day\(^{-1}\)) in children with otitis media, the drug was highly effective, even against strains with MICs of 2 μg ml\(^{-1}\) and higher (8).

For H. influenzae, there are wide variations among the β-lactams in the percentage of time above MIC achieved (Table 2). Several of the cephalosporins (e.g. cefaclor, cefuroxime and cefprozil) do not provide sufficient serum levels to achieve a 40% time above MIC, and are unlikely to exhibit high bacteriological efficacy. Using the same study as above as an example, for those patients infected with H. influenzae, the bacteriological failure rate with cefaclor was 50% compared with 27% for amoxicillin (7). However, the failure rate with amoxicillin was 60% against strains producing β-lactamase compared with 21% for β-lactamase negative strains, clearly illustrating the effect of resistance on antimicrobial efficacy (7).

**MACROLIDES**

For the older macrolides (e.g. erythromycin and clarithromycin), as for the β-lactams, time above MIC is predictive of bacteriological efficacy (3). For optimal efficacy, macrolide serum concentrations should exceed the MIC of the infecting pathogen for 40–50% of the dosing interval. Although the azalide, azithromycin, does not exhibit concentration-dependent killing, the AUC/MIC ratio correlates with bacteriological efficacy. This may be due to the much longer in vivo PAEs produced by azithromycin, in comparison with other macrolides or β-lactams (2). For azithromycin, the 24-hour AUC/MIC ratio needs to exceed

**TABLE 2. Time above MIC\(_{90}\) (T > MIC) for oral β-lactams against penicillin-susceptible (PSSP), -intermediate (PISP) and -resistant S. pneumoniae (PRSP) and H. influenzae**

<table>
<thead>
<tr>
<th>Antimicrobial Regimen (mg)</th>
<th>PSSP</th>
<th>PISP</th>
<th>PRSP</th>
<th>H. influenzae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox/clav 875/125 b.d.</td>
<td>100</td>
<td>50</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>Cefaclor 500 t.d.</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cefuroxime 500 b.d.</td>
<td>73</td>
<td>41</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Celpozil 500 b.d.</td>
<td>78</td>
<td>38</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Celpodoxime 200 b.d.</td>
<td>62</td>
<td>32</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>Cefixime 400 o.d.</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>Ceftriaxone 1000 o.d.</td>
<td>100</td>
<td>78</td>
<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>

**FIG. 2. Relationship between time above MIC\(_{90}\) and bacteriological cure for S. pneumoniae and H. influenzae in the treatment of otitis media and acute maxillary sinusitis.**

![Graph showing relationship between time above MIC and bacteriological cure for S. pneumoniae and H. influenzae.](image-url)
25 for optimal efficacy. This value is comparable to averaging one times the MIC over a 24-hour period. Although it is often argued that for macrolides tissue rather than serum levels determine efficacy, it must be remembered that the major respiratory tract pathogens are found primarily in extracellular sites. Thus, the high concentration of macrolides intracellularly decreases the potential of achieving therapeutic concentrations at the extracellular site of infection (9).

In the clinical setting, double tympanocentesis studies in pediatric AOM using erythromycin and clarithromycin have shown that standard doses of these agents produce drug serum levels which exceed the MIC$_{50}$ for susceptible strains of *S. pneumoniae* for 88–100% of the dosing interval (10). Correspondingly, the bacteriological cure rates are high—93% for erythromycin and 100% for clarithromycin (11). Against susceptible strains of *S. pneumoniae*, the AUC/MIC ratio for a standard dose of azithromycin is 50. By contrast, for macrolide-resistant strains, the AUC/MIC ratio for azithromycin is less than 0-1, predicting poor efficacy against these strains. This has been shown clinically, with a high bacteriological cure rate of 92% for azithromycin against macrolide-susceptible *S. pneumoniae* compared with only 38% against macrolide-resistant strains (8). This low rate of cure is almost the same as that observed with placebo, where around 20% of patients have spontaneous eradication of the infecting pathogen (17).

There is growing evidence that, even though MICs for macrolides against *H. influenzae* may be in the 'susceptible' range (as defined by current MIC breakpoints), in vivo bacteriological efficacy is poor against this pathogen. For example, against strains of *H. influenzae* with clarithromycin or erythromycin MICs of 4 $\mu$g $\text{ml}^{-1}$, the time above MIC would be 0% of the dosing interval for both of these agents at standard dosing regimens. For azithromycin, a similar situation has been observed. For example, against *H. influenzae* with azithromycin MICs of 0.5–2 $\mu$g $\text{ml}^{-1}$ (i.e. susceptible), the rate of bacteriological failure was as high as 61%. Moreover, when only those isolates with MICs > 2 $\mu$g $\text{ml}^{-1}$ were included, bacteriological failure increased to 78% (8). This is consistent with PK/PD predictions, as an azithromycin MIC against *H. influenzae* of 2 $\mu$g $\text{ml}^{-1}$ would give an AUC/MIC ratio of < 2, well below the value of 25 required for bacteriological efficacy.

**FLUOROQUINOLONES**

The 24 hour AUC/MIC ratio is predictive of bacteriological efficacy for the fluoroquinolones (3), and is independent of the dosing interval, the fluoroquinolone used and the site of infection (2). The magnitude of this parameter required for bacteriological efficacy varies according to the infecting pathogen—for *S. pneumoniae* AUC/MIC needs to be 25–30. In comparison, for Gram-negative bacilli (e.g. *Escherichia coli*), particularly those causing nosocomial infections, the AUC/MIC ratio needs to reach 100; that is, serum levels need to average around four times the MIC over a 24-hour period (2).

A variety of fluoroquinolones have been evaluated in animal models of infection using mortality as the endpoint. In studies involving immunocompetent animals infected with *S. pneumoniae*, there was low mortality at AUC/MIC ratios of 25 and above (13). By contrast, similar work in immunocompromised animals, where the infections were caused by various Gram-negative bacteria (*E. coli, Klebsiella spp.* and *Pseudomonas spp.*), indicated that levels of survival became significant only when AUC/MIC ratios reached 100 or above (14).

These findings are supported clinically. Two studies have investigated the relationship between PK/PD and efficacy of ciprofloxacin and levofloxacin (15,16). Forrest et al. retrospectively analyzed 64 seriously ill patients who were treated with intravenous ciprofloxacin at doses ranging from 200 mg b.d. to 400 mg t.d. (15). A population PK/PD analysis relating drug exposure to infectious outcome was determined. Data revealed that a 24-hour AUC/MIC ratio of 125 was required for favorable clinical and bacteriological outcome. For those patients who had an AUC/MIC ratio of < 125 (n = 45), however, the probability of clinical or microbiological cure was 42% and 26%, respectively (15). At an AUC/MIC ratio of ≥ 125 (n = 45), the probability of clinical cure increased to 80% (P<0.005) and microbiological cure to 82% (P<0.001), respectively. Preston et al. conducted a prospective study of 134 patients with infections of the skin or urinary or respiratory tract of mixed microbial etiology (16). Patients were treated with intravenous levofloxacin, 250–500 mg every 24 hours for at least three doses. The probability of both clinical and microbiological cure was significantly higher (P<0.001), when the peak/MIC ratio was at least 12-2. This value is comparable with a 24 hour AUC/MIC ratio of 100 (16).

**Relevance of PK/PD and NCCLS breakpoints for oral agents**

**S. PNEUMONIAE**

The value of PK/PD relationships has been recognized by the National Committee for Clinical Laboratory Standards (NCCLS) as an important factor to consider when establishing susceptibility breakpoints. New NCCLS breakpoints, issued in January 2000, for oral $\beta$-lactams for *S. pneumoniae* reflect the impact of PK/PD relationships (Table 3) (17).

For $\beta$-lactam antibiotics, only two oral agents were previously designated NCCLS breakpoints for *S. pneumoniae*—amoxicillin and cefuroxime (both 0.5 $\mu$g $\text{ml}^{-1}$). With a target PK/PD value of 40% time above MIC for predicted efficacy, a PK/PD breakpoint can be calculated. Thus, *S. pneumoniae* NCCLS susceptibility breakpoints were set at 2 $\mu$g $\text{ml}^{-1}$ for amoxicillin and 1 $\mu$g $\text{ml}^{-1}$ for cefuroxime to more accurately reflect the in vivo bacteriological efficacy of these agents. Breakpoints have also been set for cefaclor (1 $\mu$g $\text{ml}^{-1}$), cefprozil (2 $\mu$g $\text{ml}^{-1}$) and cefpodoxime (0.5–5 $\mu$g $\text{ml}^{-1}$), though as yet there is no NCCLS breakpoint for cefixime (PK/PD breakpoint 0-5 $\mu$g $\text{ml}^{-1}$).
Table 3. Pharmacodynamic (PD) and old and new NCCLS susceptibility breakpoints for various oral β-lactam antimicrobial agents with *S. pneumoniae* (17)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Old NCCLS breakpoint (µg ml⁻¹)</th>
<th>PD breakpoint (µg ml⁻¹)</th>
<th>New NCCLS breakpoint (µg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>-</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>-</td>
<td>1-2</td>
<td>2</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>-</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefixime</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The NCCLS breakpoints for both clarithromycin and erythromycin of 0.25 µg ml⁻¹ are in line with PK/PD breakpoints. For the azalide, azithromycin, in order to achieve an AUC/MIC ratio of 25, the PK/PD breakpoint for *S. pneumoniae* would be 0.12 µg ml⁻¹. This is two doubling dilutions lower than the current NCCLS breakpoint of 0.5 µg ml⁻¹.

For the fluoroquinolones, NCCLS breakpoints are only available at present for levofloxacin (2 µg ml⁻¹), ofloxacin (2 µg ml⁻¹), grepafloxacin (0.5 µg ml⁻¹) and trovafloxacin (1 µg ml⁻¹). These breakpoints are generally in line with PK/PD breakpoints calculated to achieve a 24-hour AUC/MIC ratio of 25-30.

**H. INFLUENZAE**

There are varying degrees of discrepancy between NCCLS breakpoints for *H. influenzae* and calculated PK/PD breakpoints for different antibiotic agents (Table 4). For the β-lactams, cefaclor shows the greatest difference in NCCLS versus PK/PD breakpoint. The clinical effect of this difference was shown in a recent double tympanocentesis study by Dagan et al. in patients with otitis media (18). With a dose of 40 mg kg⁻¹ day⁻¹ cefaclor, they reported a high bacteriological failure rate for *H. influenzae* of 50% (15/30). This is despite all the *H. influenzae* isolates being susceptible to cefaclor using NCCLS breakpoints (18). From these findings, the investigators determined that the clinically relevant breakpoint for cefaclor was 0.25 µg ml⁻¹, which is closer to the PK/PD breakpoint (18).

For both clarithromycin and azithromycin, the PK/PD breakpoint is five doubling dilutions lower than the NCCLS breakpoint. Again, there is evidence from studies in otitis media supporting the clinical relevance of the PK/PD parameter. For example, in the same recent study as above, 17 of 35 (49%) patients treated with 10 mg kg⁻¹ day⁻¹ azithromycin experienced bacteriological failure (18). The low bacteriological efficacy of azithromycin against *H. influenzae* has been confirmed in another recent study in which azithromycin (10 mg kg⁻¹ on day 1, then 5 mg kg⁻¹ day⁻¹ for 4 days) failed to eradicate *H. influenzae* in 61% of patients (8). In both these studies, all isolates were susceptible to azithromycin using the NCCLS breakpoint. Similar failure rates to those seen with azithromycin have also been observed for clarithromycin (19). These data indicate the lack of clinical relevance of current NCCLS breakpoints for the macrolides against *H. influenzae* in otitis media. Based on clinical data, Dagan et al. recommend a breakpoint of 0.12 µg ml⁻¹ for azithromycin against *H. influenzae*, in line with the PK/PD breakpoint (18). However, clarithromycin and azithromycin provide higher concentrations in the lungs than in middle ear fluid, which may allow higher susceptibility breakpoints when treating pulmonary infections with these drugs.

### Table 4. Pharmacodynamic (PD) and NCCLS susceptibility breakpoints for various oral antimicrobial agents with *H. influenzae*

<table>
<thead>
<tr>
<th>Drug</th>
<th>PD breakpoint (µg ml⁻¹)</th>
<th>NCCLS breakpoint (µg ml⁻¹)</th>
<th>Dilutions difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>1-2</td>
<td>8</td>
<td>4-2</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cefixime</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.25</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.25</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Elimination of resistant pathogens from the nasopharynx**

The nasopharynx acts as a reservoir of infection and a source for the dissemination of resistant isolates. Recent studies show that children treated with a course of antimicrobial medication have a greater risk of becoming carriers of non-susceptible pneumococci (20,21). Although prescribers recognize the problem of antibiotic resistance,
unnecessary or inappropriate prescription of antimicrobial agents is common (22). When the use of an antibiotic is warranted, clinicians must consider the agent’s ability to eradicate non-susceptible pathogens not only from the site of infection, but also from the nasopharynx.

A French study involving a group of children with acute otitis media evaluated the impact of 10 days’ treatment with either cefixime suspension (8 mg kg⁻¹ day⁻¹ b.d.) or amoxicillin/clavulanate suspension (80 mg kg⁻¹ day⁻¹ t.d.) on the eradication of S. pneumoniae from the nasopharynx (23). Using PK/PD parameters, amoxicillin/clavulanate would be expected to be superior in eradicating penicillin-non-susceptible S. pneumoniae. A total of 224 patients were carrying S. pneumoniae at enrollment—117 (48 PRSP) were treated with cefixime and 107 (54 PRSP) with amoxicillin/clavulanate. At end of treatment, significantly fewer children receiving amoxicillin/clavulanate were carriers of S. pneumoniae—including PRSP—compared with those receiving cefixime (21 versus 95, P < 0.001). This represents an 80% reduction in the carriage of S. pneumoniae with amoxicillin/clavulanate compared with only 19% with cefixime. Of those patients carrying S. pneumoniae at end of therapy, 48 in the cefixime group carried PRSP strains compared with just 21 patients in the amoxicillin/clavulanate group (23). This represents a 69% reduction in the carriage of PRSP with amoxicillin/clavulanate, compared with a 0% reduction in PRSP carriage with cefixime. These results are exactly in line with predictions made based on PK/PD parameters.

A study by Cohen et al. (24) compared a single, intramuscular injection of ceftriaxone (50 mg kg⁻¹) with 10 days of treatment with amoxicillin/clavulanate (10 mg kg⁻¹ day⁻¹ t.d.) on the nasopharyngeal carriage of S. pneumoniae in children with AOM. Using PK/PD parameters, both of these agents would be expected to display high bacteriological efficacy. Before treatment, 65 and 78 children receiving ceftriaxone and 71 and 80 receiving amoxicillin/clavulanate were carriers of susceptible and non-susceptible strains of S. pneumoniae, respectively. However, at the end of treatment, significantly fewer children receiving amoxicillin/clavulanate were carriers of S. pneumoniae—including PRSP—compared with those receiving ceftriaxone (41 versus 99, P < 0.0001). A total of 63 children in the ceftriaxone group were carriers of non-susceptible S. pneumoniae compared with just 34 in the amoxicillin/clavulanate group (P = 0.02). This difference may be explained to some extent by the fact that, in the case of ceftriaxone, swabs were taken from the nasopharynx at 10 days. Thus, drug levels with a single dose of ceftriaxone were above the MIC for only about 2 of the 10 days, so the duration of time above MIC was actually inferior to that obtained with amoxicillin.

Based on the data above on the eradication of nasopharyngeal carriage of PSSP and PRSP, serum concentrations need to exceed the MIC for about 80–100% of the dosing interval to achieve high rates of eradication. Current dose regimens may not be sufficient to achieve this requirement. New formulations, which deliver higher doses, are being developed to ensure that target PK/PD values can be reached. For example, a new 6-4 mg kg⁻¹ day⁻¹ suspension formulation of amoxicillin/clavulanate has been developed specifically for this purpose. Data have not yet been reported on the effect of this formulation on nasopharyngeal carriage. However, initial bacteriological efficacy results in otitis media are encouraging (25). In a recently reported study, 351 patients with AOM had pathogens isolated at screening. Overall, 54% of the 146 isolates of S. pneumoniae detected were penicillin susceptible, with 17% intermediate and 29% resistant. Of the patients with S. pneumoniae infection, 114 had repeat tympanocentesis that was positive for S. pneumoniae. Treatment with high-dose amoxicillin/clavulanate resulted in eradication of S. pneumoniae in 99% of these patients at end of therapy (23).

Inappropriate antibiotic therapy can increase the probability of continued nasopharyngeal carriage and the risk of harboring resistant strains. For example, a study conducted in children in Iceland found that the odds ratio for carriage of penicillin-resistant pneumococci, after three or more courses of antibiotic therapy, was 12 with erythromycin or co-trimoxazole, compared with only 6 for β-lactams (26). This indicates that erythromycin was a more potent selector of penicillin resistance than β-lactams in this community. This is because the particular clone of S. pneumoniae in these individuals was resistant to multiple agents. Here, the use of one antibiotic class, in this case macrolides and co-trimoxazole, can select for resistance to another classes of agent, in this case penicillin (26).

Emergence or selection of resistant mutants

The application of pharmacodynamic concepts suggests that bacterial exposure to low and prolonged concentrations of antimicrobial agents may have a role in the selection of resistant strains. Analysis of macrolide prescribing and resistance patterns in S. pneumoniae indicates a correlation between increasing macrolide resistance and the use of newer, long-acting macrolides (e.g. azithromycin and clarithromycin) (27). These agents have long half-lives, and serum concentrations do not exceed the MIC throughout the dosing interval. This may increase the potential for the induction of antibiotic resistance. Further evidence of the impact that macrolides may have on resistance development comes from Iceland (28). As discussed above, in this country, the predominant drug-resistant S. pneumoniae clone (type 6B) is multi-resistant to a number of agents and macrolides have been shown to select for penicillin resistance in this organism (26). The consumption of macrolides and co-trimoxazole has fallen by 30% since 1990. This has coincided with a decrease in penicillin-resistant S. pneumoniae from a peak prevalence of 20% in 1992 to 13% in 1997 (28). There was no major change in the use of β-lactams during this period (< 10%).

Various PK/PD parameters have been proposed as indicators for the potential of antibiotics to induce resistance mutations. For example, for fluoroquinolones,
the ratio between the peak serum concentration and the MIC, termed the inhibitory quotient, may be relevant. The higher the inhibitory quotient, the lower the potential for resistance selection—the inhibitory quotient lower than 4 is thought to indicate a high potential for resistance selection. Recent interest has been directed towards experiments to determine the mutation prevention concentration (MPC). This is the lowest concentration of drug that will prevent selection of any mutants in very large inocula. Initial studies suggest that the magnitude of the MPC varies according to the organism and to the antimicrobial agent used (29). Generally, MPC values for fluoroquinolones range from 4 to 10 times the MIC. Previous studies in humans and in animal models of infection have demonstrated that peak concentrations of 8–10 times the MIC can prevent the emergence of resistant mutants (30,31).

Conclusion

The PK/PD parameters are useful for predicting antibiotic efficacy in RTIs and can, therefore, be used in a variety of ways to optimize the use of these agents. They provide a valuable basis for recommendations in therapeutic guidelines, such as the DRSP Working Group guidelines for otitis media (32), pneumonia (33) and the recent American Academy of Otolaryngology, Head and Neck Surgery sinusitis guidelines (34) and have a key role to play in establishing susceptibility breakpoints, as witnessed by their inclusion in recent NCCLS criteria for establishing new breakpoints for S. pneumoniae (17).

It is now well accepted that currently available antibiotics vary significantly in their ability to achieve the PK/PD values necessary for bacterial eradication, particularly in the case of resistant strains. Appropriate antimicrobial choice (choice of agent, dose and duration) should be based on the ability to eradicate pathogens from the site of infection and from the nasopharynx using PK/PD principles and local susceptibility data as a guide to effective therapy.

In conclusion, the judicious use of antimicrobial agents should permit the clinician to prescribe from a selection of agents which maximize bacteriological and clinical cure, and which minimize the emergence and spread of resistant pathogens.

References


