

Combating resistance: application of the emerging science of pharmacokinetics and pharmacodynamics

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Abstract

During the last 10–15 years understanding of relationships between pharmacokinetic (PK) and pharmacodynamic (PD) parameters and bacteriological and clinical outcomes has expanded allowing correlation between in vitro potency and in vivo efficacy. PK and PD principles can be applied to development of new antibacterials and formulation of existing agents to help address the increasing prevalence of antibacterial resistance. For beta-lactams, such as penicillins, the unbound serum concentration of the drug exceeding the minimum inhibitory concentration of the causative pathogen for 40–50% of the dosing interval is predictive of bacteriologic efficacy (bacterial eradication) and can be used to determine a PK/PD breakpoint for that specific dosing regimen. Amoxicillin/clavulanate was one of the earliest antibacterials to use the unique approach of PK/PD principles to develop new and enhanced formulations, allowing it to remain a significant antibacterial agent in the management of respiratory tract infections.

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1. Introduction

The introduction of antimicrobial agents over 60 years ago has had an enormous effect on the outcome of bacterial infections, greatly reducing both morbidity and mortality. Of particular significance are respiratory tract infections (RTIs), leading infectious causes of morbidity and mortality. Increased antibacterial resistance amongst the three major respiratory pathogens – *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* – has compromised the efficacy of several oral antibacterials widely used for the treatment of RTIs.

It is thus increasingly important to find ways to maximise antibacterial efficacy in RTIs by re-evaluating the therapeutic choices available. Few new classes of antibacterials have been introduced in recent years, and optimising dosing regimens and development of new formulations of existing antibacterials are alternative options.

2. Clinical significance of in vitro susceptibility

Until recently, the antibacterial efficacy of an antibiotic was assessed by in vitro measurements of its minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against specific bacteria without regard for clinically achievable concentrations. These values do not account for fluctuations of drug levels within the body or over the time frame of the dosing period and so cannot give a true picture of the clinical efficacy of that antibiotic. In vivo bacteriologic outcome is the best measure of in vivo efficacy but this is only possible in certain diseases such as otitis media, sinusitis and meningitis. Double tympanocentesis studies in paediatric otitis media, in which the middle ear fluid is sampled and tested both before and during treatment, for example, give an accurate picture of bacteriologic outcome and bacterial eradication [1].

During the last 10–15 years, however, understanding of the relationships between pharmacokinetic (PK) and pharmacodynamic (PD) parameters and bacteriological and clinical outcomes has expanded so that they can now allow us to correlate in vitro potency more closely with in vivo efficacy.

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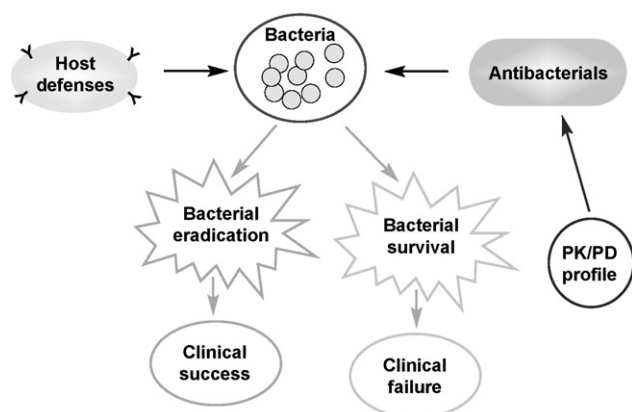


Fig. 1. Determinants of clinical outcome [2,3].

This means that it is now possible to use PK/PD principles to assist in the development of new antibiotics and formulations, optimisation of existing formulations and rationalisation of therapy choices.

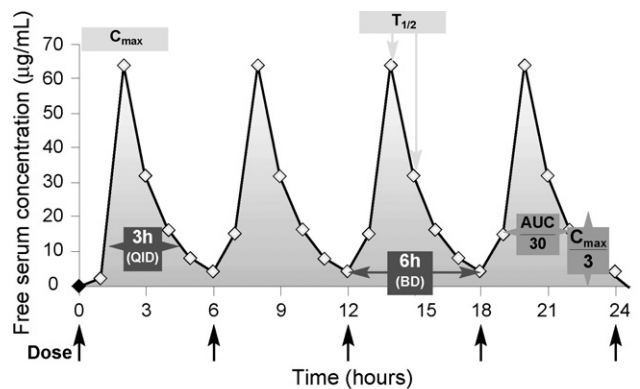
3. Determinants of clinical outcome

Most infections are self-limiting and resolve spontaneously as a result of intrinsic host defences, although use of active antibacterial agents results in earlier resolution of disease. Only when the defences of the host are inadequate are we reliant on antibacterial agents to cure the infection. The PK/PD profile of the antibacterial agent within the host can be used to predict the likelihood of bacterial efficacy based on the activity of antibacterial agents (Fig. 1) [2,3].

4. Evaluating antimicrobial efficacy

Both PK and PD characteristics influence *in vivo* antimicrobial efficacy. PK includes the serum concentration profile of the antibiotic over time and its penetration to the site of infection. PD parameters include the relationship between serum concentration and drug pharmacology and toxicology, bacterial susceptibility and killing and persistent (post-antibiotic) effects [2]. It is the PK/PD relationship for an antibiotic that is important in understanding both drug dose and antibacterial efficacy.

There are three major PK/PD patterns of antibacterial activity (Table 1) [3]. For time-dependent killing with minimum to moderate persistent effects (for example



C_{max} , peak concentration; $T_{1/2}$, half life, BD, twice daily dosing; QID, four times daily dosing

Fig. 2. Free serum pharmacokinetics for a drug dose achieving a peak concentration (C_{max}) of 64 mg/L, time to peak of 2 h, half-life ($T_{1/2}$) of 1 h and AUC_{0-24} of 480 mg h/L.

cephalosporins and penicillins), the dosing regimen must maximise the time above the MIC of the antibiotic against the pathogen. For beta-lactams, an unbound (nonprotein bound) drug serum concentration exceeding the MIC for more than 20–50% of the dosing interval is predictive of bacteriologic efficacy against respiratory pathogens (20% for carbapenems, 40% for penicillins and 50% for cephalosporins).

Macrolides and azalides exhibit time-dependent killing and prolonged persistent effects, with the ratio of the area under the 24-hour time–concentration curve (AUC_{0-24}) for unbound drug to the MIC (AUC_{0-24}/MIC ratio) predicting outcome most accurately. For agents with concentration-dependent killing and prolonged persistent effects, such as the fluoroquinolones, the 24-hour unbound serum AUC/MIC ratio and the peak unbound serum level/MIC ratio both correlate with efficacy, with ratios of ≥ 30 and ≥ 3 , respectively, required for efficacy with Gram-positive infections. The total amount of drug administered is the critical determinant of efficacy of concentration-dependent agents.

To illustrate these parameters, Fig. 2 shows PK values for a drug dose that produces a peak concentration of 64 mg/L, time to peak of 2 h, half-life of 1 h and 24-h AUC (AUC_{0-24}) of 480 mg h/L. If the drug is a cephalosporin and is dosed every 6 h a free serum concentration of ≥ 12 mg/L would be present for 3 h (50% of the dosing interval). If the same dose was administered every 12 h a free serum concentration of only around 4 mg/L would be present for 50% of the dosing interval as this is now 6 h. PK/PD parameters may thus be utilised to provide the link between dose, dosing interval and MIC of the target pathogen. Therefore,

Table 1
Pharmacodynamic patterns of antibacterial activity [3]

| Pattern | Pharmacodynamic correlate |
|---|--|
| Time-dependent killing and minimal to moderate persistent effects | Time above MIC ($T > MIC$) > 40 –50% of dosing interval* |
| Time-dependent killing and prolonged persistent effects | AUC/MIC ratio $> 30^*$ |
| Concentration-dependent killing and prolonged persistent effects | AUC/MIC ratio $> 30^*$ or Peak/MIC ratio $> 3^*$ |

* All correlations are based on nonprotein bound serum levels. MIC, minimum inhibitory concentration; AUC, area under the plasma concentration curve.

infections caused by organisms with MICs of up to 4 mg/L could be successfully treated with both dosing regimens of this cephalosporin; only the 6-hourly dosing regimen would be effective against organisms with MICs of 8 mg/L, while organisms with MICs ≥ 16 mg/L would be resistant to both dosing regimens. If, however, this agent is a fluoroquinolone administered four times a day, it would be effective against organisms with MICs up to 16 mg/L based on AUC_{0-24}/MIC ratio of 30 or peak/MIC ratio of 3 being required for efficacy.

5. PK/PD breakpoints

If the PK/PD parameter is known, then the PK/PD susceptibility breakpoint up to which in vivo activity is predicted can be determined for a given dosing regimen. For time-dependent agents, the PK/PD breakpoint is the free serum concentration present for the appropriate percentage of the dosing interval (20% for carbapenems, 40% for penicillins and 50% for cephalosporins). The PK/PD breakpoint is the same for all the major organisms associated with RTIs, but differs by antibacterial and dosing regimen (Table 2).

5.1. Application of PK/PD breakpoints to Alexander Project results

The Alexander Project was a 10-year global multicentre surveillance study set up in 1992 to investigate the antimicrobial susceptibility of community-acquired pathogens implicated in RTIs [5,6]. Bacterial isolates submitted to a central laboratory were identified and tested for antimicrobial susceptibility against 16 antibiotics. Data from the study have provided a resource for measuring trends in the susceptibility patterns of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Between 1992 and 2001, susceptibility of *S. pneumoniae* isolates from five European countries and the USA based on PK/PD breakpoints varied from country to country and changed considerably with time (Fig. 3) [7]. In Germany, for example, the susceptibility of *S. pneumoniae* remained close

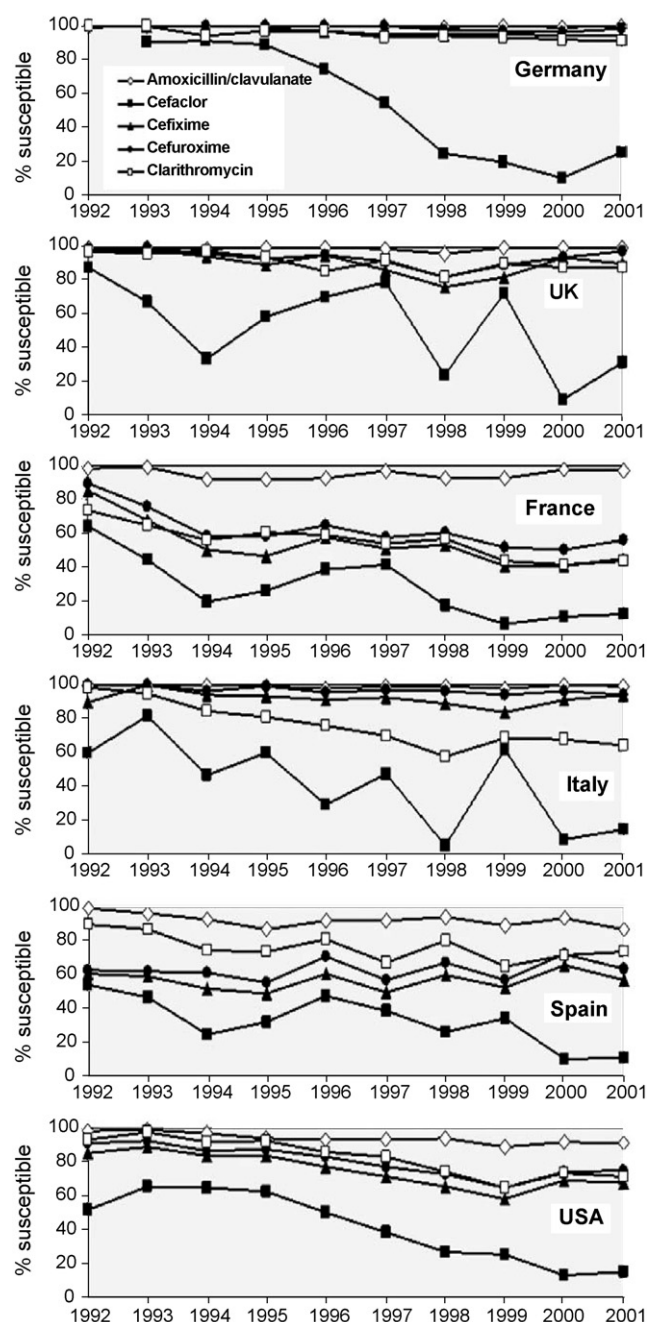


Fig. 3. Susceptibility of five representative agents for *S. pneumoniae* from six countries participating in the Alexander Project, 1992–2001 [7]. Susceptibility of amoxicillin was very similar to amoxicillin/clavulanate, while that of azithromycin and erythromycin was very similar to clarithromycin.

to 100% for amoxicillin, amoxicillin/clavulanate, cefixime, cefuroxime, erythromycin, clarithromycin and azithromycin but the percent susceptibility to cefaclor had dropped to below 30% by 1998. A similar picture was seen for the UK susceptibility data. In France, Italy, Spain and the USA, although susceptibilities to amoxicillin and amoxicillin/clavulanate remained at around 90–100%, the figures for the other antibacterials tested fell gradually during the 10-year period, most prominently for cefaclor.

Table 2

Breakpoints based on PK and PD parameters for selected oral and parenteral beta-lactams [4]

| | PK/PD breakpoint (mg/L) |
|-------------------------|-------------------------|
| Amoxicillin | 2/4* |
| Amoxicillin/clavulanate | 2/4* |
| Cefuroxime axetil | 1 |
| Cefuroxime sodium** | 4 |
| Cefprozil | 1 |
| Cefixime | 1 |
| Cefaclor | 0.5 |
| Ceftriaxone** | 2 |
| Cefdinir | 0.5 |

PK, pharmacokinetics; PD, pharmacodynamics.

* 2 mg/L for lower and 4 mg/L for higher dosing regimens.

** Parenteral agents.

Table 3

Bacteriologic eradication of major acute otitis media pathogens with regular and high-dose amoxicillin/clavulanate on days 4–6 of therapy

| Amoxicillin/clavulanate dose (in 2 divided doses per day) | Bacteriologic eradication on day 4–6 of therapy (%) | | | Reference |
|---|---|-------------------------------|---------------|-----------|
| | <i>Streptococcus pneumoniae</i> | <i>Haemophilus influenzae</i> | All pathogens | |
| 40/6.4 mg/kg/d | 90 | 87 | 83 | [1] |
| 90/6.4 mg/kg/d | 96 | 90 | 94 | [9] |
| 90/6.4 mg/kg/d | 98 | 94 | 96 | [10] |

6. Development of amoxicillin/clavulanate dosage regimens

Amoxicillin/clavulanate was one of the first drugs to use the unique approach of PK/PD principles in the development of high-dose and PK-enhanced formulations for children and adults. These formulations were designed to eradicate *S. pneumoniae*, including penicillin-resistant strains with amoxicillin MICs as high as 4 mg/L. Human PK and variability were determined along with the MIC distribution of the target pathogens, and modified dosage regimens were simulated to produce sufficient target attainments. Information gained from this approach led to the development of a high-dose paediatric formulation of amoxicillin/clavulanate (Augmentin ES-600) in which the daily dose of amoxicillin/clavulanate was increased from 45/6.4 mg/kg/day to 90/6.4 mg/kg/day, extending the concentration present for 40% of the dosing interval from 2 mg/L to 4 mg/L. For adults a sustained release formulation of amoxicillin/clavulanate (Augmentin SR), containing 2000 mg of immediate and sustained release amoxicillin in one tablet, extended the serum concentration of amoxicillin above the target MIC of 4 mg/L for >40% of the dosing interval (Fig. 4). The sustained release formulation extends the time that the free serum concentration of the drug is above 4 mg/L to 49% of the dosing interval, whereas 2000 mg of an immediate release formulation only achieves

a concentration of 2 mg/L for >40% of the dosing interval [8].

7. In vivo demonstration of efficacy of high-dose amoxicillin/clavulanate in acute otitis media

The superiority of high-dose amoxicillin/clavulanate (90/6.4 mg/kg/day in two divided doses) over 45/6.4 mg/kg/day in two divided doses was demonstrated in vivo in children with acute otitis media [1,9,10]. Eradication of pathogens on days 4–6 of therapy increased from 83% with the lower dosing regimen to 94–96% with the high-dose regimen, with improvement in clinical outcome as well as in eradication rates of both major AOM pathogens, *S. pneumoniae* and *H. influenzae* (Table 3).

8. Conclusions

PK/PD principles provide a mechanism to correlate in vitro potency with in vivo efficacy of antibacterials. Application of these principles has allowed us to document clinically relevant changes in antimicrobial susceptibility over time, showing, for example, development of resistance in *S. pneumoniae* isolates in the Alexander Project. PK/PD principles can also be applied in the development of new formulations of existing drugs, for example, in the development of new formulations of amoxicillin/clavulanate, allowing its continued clinical use, particularly in RTIs, 25 years after its first launch.

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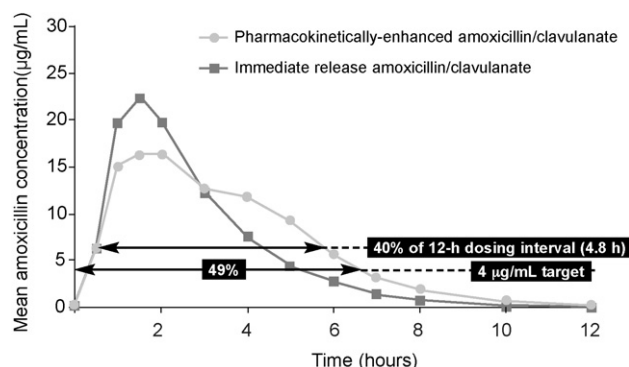


Fig. 4. Mean plasma concentration – time profile for amoxicillin after oral administration of amoxicillin/clavulanate formulations containing 2000 mg of immediate release amoxicillin and 2000 mg of a pharmacokinetically enhanced formulation containing 1125 mg of immediate and 875 mg of sustained release amoxicillin [8]. 'Redrawn from Kaye CM, et al. The clinical pharmacokinetics of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate. Clin Ther 2001;4:578–84, with permission from Excerpta Medica.

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References

- [1] Dagan R, Johnson CE, McLinn S, et al. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs azithromycin in acute otitis media. *Pediatr Infect Dis J* 2000;19:95–104.
- [2] Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β -lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am* 2003;17:479–501.
- [3] Jacobs MR. Anti-infective pharmacodynamics –maximizing efficacy, minimizing toxicity. *Drug Discov Today* 2004;1: 505–12.
- [4] Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2004;130:1–45.
- [5] Grüneberg RN, Felmingham D. The Alexander Project Group. Results of the Alexander Project: a continuing multicenter study of the antimicrobial susceptibility of community-acquired lower respiratory tract bacterial pathogens. *Diagn Microbiol Infect Dis* 1996;25: 169–81.
- [6] Jacobs MR, Felmingham D, Appelbaum PC, Grüneberg RN. The Alexander Project Group. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother* 2003;52:229–46.
- [7] Felmingham D, White AR, Jacobs MR, et al. The Alexander Project: the benefits from a decade of surveillance. *J Antimicrob Chemother* 2005;56:3–21.
- [8] Kaye CM, Allen A, Perry S, et al. The clinical pharmacokinetics of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate. *Clin Ther* 2001;23:578–84.
- [9] Hoberman A, Dagan R, Leibovitz E, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *Pediatr Infect Dis J* 2005;24:525–32.
- [10] Dagan R, Hoberman A, Johnson C, et al. Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. *Pediatr Infect Dis J* 2001;20: 829–37.