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Pharmacokinetics and pharmacodynamics of oral β-lactam antibiotics as a two-dimensional approach to their efficacy

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Pharmacokinetic and pharmacodynamic parameters are increasingly recognized as important determinants of the therapeutic efficacy of an antibiotic. For β-lactam antibiotics, the most important determinant of the antimicrobial efficacy, and hence predictor of therapeutic efficacy, is the length of time that serum concentrations exceed the MIC. Dosing schedules for β-lactam antibiotics should maintain serum concentrations above the MIC for the bacterial pathogen for at least 50% of the dosing interval to achieve therapeutic efficacy and prevent the development of resistance. This is a basic criterion for the clinical efficacy of β-lactams. A combination of microbiological activity and pharmacokinetic characteristics was applied to calculate the time that serum antibiotic concentrations exceed the MIC for the major respiratory tract pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes* and *Klebsiella pneumoniae*. In contrast with some other oral β-lactam antibiotics, cefpodoxime 200 mg bd maintains serum concentrations above the MIC for each organism for at least 50% of the dosing interval and may therefore be an attractive choice for empirical therapy of community-acquired lower respiratory tract infections.

Introduction

The global emergence and spread of bacterial resistance increase the risk of clinical failure of antibiotics. *Streptococcus pneumoniae* is a major pathogen in respiratory tract infection. The worrying increase in the prevalence of resistance among *S. pneumoniae* to penicillins and macrolides, as shown by the Alexander Project[1] and other surveys, has prompted concern about options for antibiotic treatment. Alternative treatments are needed with sufficient potency and favourable pharmacokinetic characteristics to achieve clinical efficacy against relevant bacterial pathogens. It is therefore increasingly important to use suitable parameters to determine the efficacy of antibiotics, and to be able to correlate them with the clinical outcome.

Pharmacokinetic and pharmacodynamic parameters relevant of the efficacy of β-lactam antibiotics

The aim of antibiotic treatment is to maximize antibacterial activity to prevent recurrence of infection and the creation of resistant pathogens.[2] Pharmacokinetic characteristics and the dosing regimen of the antibiotic determine the time course of serum antibiotic concentrations. The pharmacodynamic characteristics of antibiotics are the second factor used in integrated pharmacokinetic/pharmacodynamic (PK/PD) models. The value of different PK/PD parameters in predicting eradication of causative bacterial pathogens has been investigated in various animal and clinical studies. For β-lactam antibiotics, the most important determinant of antibacterial efficacy and predictor of therapeutic efficacy is the length of time that serum concentrations exceed the MIC.[3] The time for which the antibiotic concentration exceeds the MIC, when expressed as a percentage of the dosing interval, is referred to as the coverage (the dosing interval itself being 100%). It has become clear that dosing schedules for β-lactam antibiotics should, as a basic criterion, maintain serum concentrations above the MIC for the more common respiratory tract pathogens for at least 50% of the dosing interval, as discussed elsewhere.[4,5] Favourable pharmacokinetics and a low MIC are therefore essential for optimal therapeutic efficacy.

Comparison of time above MIC for β-lactam antibiotics

Integration of antibacterial activity and pharmacokinetic properties allows the prediction of the time that serum anti-

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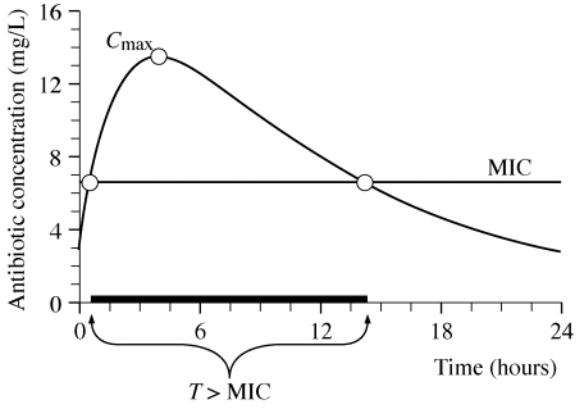

Figure 1. Calculation of the pharmacokinetic/pharmacodynamic relationship is dependent on the elimination half-life and the MIC. β-lactams: $T > \text{MIC}\ (T_{persistence}) = T_{½} \times \ln (C_{max}/\text{MIC}) / \ln(2) + T_{max}$; where C_{max} is the peak plasma concentration, $T_{½}$ is the elimination half-life, T_{max} is the time after dosing for peak concentration to be reached, and $T >$ MIC is the time above minimum inhibitory concentration. (A similar approach is discussed further in Turnidge.[5])

biotic concentrations will exceed the MIC for a bacterial pathogen. Using data from current reference sources for *in vitro* antibacterial activity[6,7] and pharmacokinetic parameters,[8–13] the time for which serum concentrations exceed the MIC for common respiratory tract bacteria has been calculated for a range of β-lactams, including cefpodoxime, ceftibuten, cefixime, cefuroxime, cefprozil, cefaclor and co-amoxiclav at standard dosing regimens. The data reflect the recommended dosing intervals for the treatment of community-acquired respiratory tract infections. Such calculations show whether or not an antibiotic is fulfilling the therapeutic efficacy criterion described above (Figure 1).

Streptococcus pneumoniae (Table 1)

Except for ceftibuten 400 mg od, serum concentrations of all other β-lactams subjected to the calculations exceed the MIC_{90} for penicillin-susceptible strains of *S. pneumoniae* for times ranging from just under 50% of the dosing interval to far above 50%. Against penicillin-intermediate strains of *S. pneumoniae*, however, serum concentrations of cefaclor 500 mg tds and cefixime 400 mg od are also below the MIC_{90} for more than 50% of the dosing interval. It is likely therefore that, under the assumption of this model, these cephalosporins would be clinically ineffective with regard to the strains in question. Like co-amoxiclav, which is regarded as standard empirical therapy for respiratory tract infections, dosing with cefpodoxime 200 mg bd maintains serum concentrations above the MIC_{90} over the complete dosing interval in the case of penicillin-susceptible *S. pneumoniae* and for more than 50% of the dosing interval in the case of penicillin-intermediate *S. pneumoniae*. Cefpodoxime would therefore be predicted to be clinically effective against penicillin-susceptible and -intermediate strains of *S. pneumoniae*.

Table 1. Comparison of times that serum concentrations of β-lactam antibiotics exceed MIC_{90} for penicillin-susceptible and -intermediate strains of *S. pneumoniae*

Antibiotic	Dose (mg)	Dosing interval (h)	C_{max} (mg/L)	$T_{½}$ (h)	T_{max} (h)	MIC_{90} (mg/L)	$T > MIC_{90}$ (h)	Coverage (%)
Penicillin-susceptible								
co-amoxiclav	3×500/125	8	7.2	1.3	1.5	0.125	9.1	113.8
cefaclor	3×500	8	15.2	0.75	1	1	3.9	49.3
cefprozil[a]	2×500	12	10.5	1.3	1.5	0.25	8.5	70.9
cefuroxime	2×500	12	7	1.2	3	0.25	8.8	73.1
cefpodoxime	2×200	12	2.6	2.4	3	0.125	13.5	112.6
cefixime	1×400	24	3.7	4	4	1	11.6	48.1
ceftibuten	1×400	24	15	2.4	2.6	8	4.8	19.9
Penicillin-intermediate								
co-amoxiclav	3×500/125	8	7.2	1.3	1.5	1	5.2	65.0
cefaclor	3×500	8	15.2	0.75	1	16	0.9	11.8
cefuroxime	2×500	12	7	1.2	3	2	5.2	43.1
cefpodoxime	2×200	12	2.6	2.4	3	1	6.3	52.6
cefixime	1×400	24	3.7	4	4	16	0.0	0.0
ceftibuten	1×400	24	15	2.4	2.6	16	2.4	9.9

[a]All strains: no differentiation between penicillin-susceptible, -intermediate or -resistant strains.
C_{max}, peak plasma concentration; $T_{½}$, elimination half-life; T_{max}, time after dosing for peak concentration to be reached; $T > MIC_{90}$, time above minimum inhibitory concentration; coverage (%) = (time above MIC/dosing interval)× 100.

Table 2. Comparison of times that serum concentrations of β-lactam antibiotics exceed MIC_{90} for β-lactamase-positive and -negative strains of *H. influenzae*

Antibiotic	Dose (mg)	Dosing interval (h)	C_{max} (mg/L)	$T_{½}$ (h)	T_{max} (h)	MIC_{90} (mg/L)	$T > MIC_{90}$ (h)	Coverage (%)
β-Lactamase-positive								
co-amoxiclav	3×500/125	8	7.2	1.3	1.5	1	5.2	65.0
cefaclor	3×500	8	15.2	0.75	1	32	0.2	2.4
cefprozil	2×500	12	10.5	1.3	1.5	6.9	2.3	19.1
cefuroxime	2×500	12	7	1.2	3	2	5.2	43.1
cefpodoxime	2×200	12	2.6	2.4	3	0.25	11.1	92.6
cefixime	1×400	24	3.7	4	4	0.25	19.6	81.5
ceftibuten	1×400	24	15	2.4	2.6	0.25	16.8	69.9
β-Lactamase-negative								
co-amoxiclav	3×500/125	8	7.2	1.3	1.5	1	5.2	65.0
cefaclor	3×500	8	15.2	0.75	1	16	0.9	11.8
cefprozil	2×500	12	10.5	1.3	1.5	2	4.6	38.4
cefuroxime	2×500	12	7	1.2	3	2	5.2	43.1
cefpodoxime	2×200	12	2.6	2.4	3	0.25	11.1	92.6
cefixime	1×400	24	3.7	4	4	0.25	19.6	81.5
ceftibuten	1×400	24	15	2.4	2.6	0.25	16.8	69.9

C_{max}, peak plasma concentration; $T_{½}$, elimination half-life; T_{max}, time after dosing for peak concentration to be reached; $T > MIC_{90}$, time above minimum inhibitory concentration; coverage (%) = (time above MIC/dosing interval)× 100.

Table 3. Comparison of times that serum concentrations of β-lactam antibiotics exceed MIC_{90} for β-lactamase-positive strains of *Moraxella catarrhalis*

Antibiotic	Dose (mg)	Dosing interval (h)	C_{max} (mg/L)	$T_{½}$ (h)	T_{max} (h)	MIC_{90} (mg/L)	$T > MIC_{90}$ (h)	Coverage (%)
Co-amoxiclav	3×500/125	8	7.2	1.3	1.5	0.25	7.8	97.5
Cefaclor	3×500	8	15.2	0.75	1	1	3.9	49.3
Cefprozil	2×500	12	10.5	1.3	1.5	2	4.6	38.4
Cefuroxime	2×500	12	7	1.2	3	2	5.2	43.1
Cefpodoxime	2×200	12	2.6	2.4	3	0.5	8.7	72.6
Cefixime	1×400	24	3.7	4	4	0.5	15.6	64.8
Ceftibuten	1×400	24	15	2.4	2.6	4	7.2	29.9

C_{max}, peak plasma concentration; $T_{½}$, elimination half-life; T_{max}, time after dosing for peak concentration to be reached; $T > MIC_{90}$, time above minimum inhibitory concentration; coverage (%) = (time above MIC/dosing interval) × 100.

Other common respiratory tract pathogens

For *Haemophilus influenzae* (β-lactamase-positive and -negative strains) (Table 2), serum concentrations of cefprozil 500 mg bd and cefaclor 500 mg tds are below the MIC_{90} for more than 50% of the dosing interval and therefore these drugs are unlikely to show high clinical efficacy against this pathogen. Cefuroxime 500 mg bd shows borderline values. More advanced cephalosporins, however, as well as co-amoxiclav, exceed the MIC_{90} for more than 50% of their dosing intervals.

Co-amoxiclav, cefpodoxime and cefixime clearly exceed the MIC_{90} for *Moraxella catarrhalis* for more than 50% of their dosing intervals (Table 3). Ceftibuten shows the lowest value, lying clearly below the 50% limit, suggesting that it might be clinically ineffective against this pathogen.

On the basis of the PK/PD model, cefpodoxime, cefixime and ceftibuten are likely to be effective against *Klebsiella pneumoniae* (Table 4), an infrequent but dangerous pathogen in respiratory tract infection in patients with concomitant risk factors such as chronic obstructive lung disease. Cefaclor,

Table 4. Comparison of times that serum concentrations of β-lactam antibiotics exceed MIC_{90} for *Klebsiella pneumoniae*

Antibiotic	Dose (mg)	Dosing interval (h)	C_{max} (mg/L)	$T_{½}$ (h)	T_{max} (h)	MIC_{90} (mg/L)	$T > MIC_{90}$ (h)	Coverage (%)
Co-amoxiclav	3 × 500/125	8	7.2	1.3	1.5	8	1.3	16.3
Cefaclor	3 × 500	8	15.2	0.75	1	8	1.7	21.2
Cefprozil	2 × 500	12	10.5	1.3	1.5	3.1	3.8	31.6
Cefuroxime	2 × 500	12	7	1.2	3	8	2.8	23.1
Cefpodoxime	2 × 200	12	2.6	2.4	3	0.5	8.7	72.6
Cefixime	1 × 400	24	3.7	4	4	0.25	19.6	81.5
Ceftibuten	1 × 400	24	15	2.4	2.6	0.25	16.8	69.9

C_{max}, peak plasma concentration; $T_{½}$, elimination half-life; T_{max}, time after dosing for peak concentration to be reached; $T > MIC_{90}$, time above minimum inhibitory concentration; coverage (%) = (time above MIC/dosing interval) × 100.

cefprozil, cefuroxime and co-amoxiclav are likely to be ineffective because they do not meet the basic criterion.

All the β-lactams included in this analysis maintained serum concentrations above the MIC_{90} for *Streptococcus pyogenes* for at least 50% of the dosing interval.

Discussion

Prolonged bacterial exposure to sub-inhibitory plasma concentrations of an antibiotic is one of the reasons for the emergence and spread of bacterial resistance. For example, the increase in macrolide resistance in Spain has been associated with an increasing use of newer macrolides with a long half-life (azithromycin), which were used in short-term therapy.[14]

Accurate PK/PD modelling is useful in predicting antibiotic efficacy in respiratory tract infection. Application of PK/PD models suggests that cefpodoxime 200 mg bd would be an attractive option for the treatment of community-acquired respiratory infections involving the major respiratory pathogens: *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. In contrast, other cephalosporins, such as cefaclor 500 mg tds and cefixime 400 mg od, for which serum levels are not maintained above the MIC for these pathogens for at least 50% of the dosing interval, are not likely to be as clinically effective as cefpodoxime. Findings from clinical trials provide support for the predictions of the PK/PD models. In a multicentre, double-blind study in adult out-patients with acute sinusitis, clinical cure rates were significantly higher with cefpodoxime than cefaclor (84% versus 68%, $P = 0.01$).[15] Cefpodoxime was also significantly better than cefaclor with respect to the rate of symptom resolution in patients with community-acquired pneumonia: 43% versus 6.7%, respectively, had evidence of symptom resolution at 3 days ($P < 0.001$).[16] In addition, Cohen *et al.*[17] showed that clinical success rates (i.e. cure and improvement) in paediatric acute otitis media were significantly higher with cefpodoxime than cefixime (88% versus 73%, $P < 0.05$).

The importance of PK/PD models in predicting the clinical efficacy of antibiotics has now been recognized in treatment guidelines for acute otitis media, pneumonia and sinusitis.[18–20] Such models may also be helpful in reconsidering breakpoint recommendations in relation to interpretive categories for the susceptibility of bacterial pathogens. The application of PK/PD models not only helps to optimize antibiotic treatment of respiratory tract infections, but may also help to prevent the spread of bacterial resistance. Other factors that may influence clinical efficacy include protein binding, variability in pharmacokinetics, and the influence of formulation and dosage regimen on compliance.

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