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Comparison of antimicrobial pharmacokinetic/pharmacodynamic breakpoints with EUCAST and CLSI clinical breakpoints for Gram-positive bacteria

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ABSTRACT

This study compared the susceptibility breakpoints based on pharmacokinetic/pharmacodynamic (PK/PD) models and Monte Carlo simulation with those defined by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for antibiotics used for the treatment of infections caused by Gram-positive bacteria. A secondary objective was to evaluate the probability of achieving the PK/PD target associated with the success of antimicrobial therapy. A 10 000-subject Monte Carlo simulation was executed to evaluate 13 antimicrobials (47 intravenous dosing regimens). Susceptibility data were extracted from the British Society for Antimicrobial Chemotherapy database for bacteraemia isolates. The probability of target attainment and the cumulative fraction of response (CFR) were calculated. No antibiotic was predicted to be effective (CFR ≥ 90%) against all microorganisms. The PK/PD susceptibility breakpoints were also estimated and were compared with CLSI and EUCAST breakpoints. The percentages of strains affected by breakpoint discrepancies were calculated. In the case of β-lactams, breakpoint discrepancies affected <15% of strains. However, higher differences were detected for low doses of vancomycin, daptomycin and linezolid, with PK/PD breakpoints being lower than those defined by the CLSI and EUCAST. If this occurs, an isolate will be considered susceptible based on CLSI and EUCAST breakpoints although the PK/PD analysis predicts failure, which may explain treatment failures reported in the literature. This study reinforces the idea of considering not only the antimicrobial activity but also the dosing regimen to increase the probability of clinical success of an antimicrobial treatment.

1. Introduction

The resistance rates of Gram-positive bacteria, in particular meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *S. aureus*, vancomycin-resistant *S. aureus*, vancomycin-resistant enterococci (VRE) and multidrug-resistant *Streptococcus pneumoniae*, are a major public health problem worldwide. Among the interventions to mitigate the current and future impact of antimicrobial resistance, the development of new generations of antimicrobials is one of the most accepted. Another recognised strategy to diminish antibiotic resistance is optimisation of the dosing regimen of available antimicrobials [1].

To maximise the likelihood of a favourable clinical/microbiological response as well as to minimise the probability of exposure-related toxicity, pharmacokinetic/pharmacodynamic (PK/PD) modelling represents a very useful tool for dose decision-making. Use of Monte Carlo simulation provides an estimate of an antibiotic dosing regimen's probability of achieving the targeted pharmacodynamic exposure, given uncertainty in patient pharmacokinetics and the minimum inhibitory concentration (MIC) distribution of the bacterial population [2]. Based on Monte Carlo simulation, we showed differences in the probability of success of several dosing regimens of vancomycin, linezolid, daptomycin and tigecycline for the treatment of MRSA infections in four Western European countries owing to differences in susceptibility patterns [3]. Another application of PK/PD analysis and Monte Carlo simulation is the establishment of breakpoints based on the likelihood of obtaining a targeted exposure [4]. Pharmacodynamics is considered by regulatory agencies for the development of susceptibility breakpoints to be used by clinical microbiology laboratories to categorise organisms as susceptible or resistant. However, divergences between the probability of pharmacodynamic target attainment and current susceptibility

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Table 1
Pharmacokinetic parameters for each antimicrobial agent from published studies among healthy adult volunteers (mean ± standard deviation).

Antimicrobial agent and dosing regimen	Administration	CL_t (mL/min)	V_{ss} (L/kg)	AUC_{SS} (mg h/L)	PB (%)
Amoxicillin [9]					
1 g q6h	0.5-h infusion	237.20 ± 44.17	0.31 ± 0.09	–	20
1 g q8h					
2 g q6h					
2 g q8h					
Cloxacillin [10]					
1 g q6h	Bolus and 1-h infusion	152.8 ± 29.1	0.10 ± 0.02	–	78
1 g q4h					
2 g q6h					
2 g q4h					
Piperacillin/tazobactam [11]					
4 g q6h	0.5-h infusion	170.4 ± 35.3	0.15 ± 0.02	–	30
4 g q8h					
Cefotaxime [12]					
1 g q6h	Bolus, 0.5-h and 1-h infusion	275.33 ± 50.11	0.207 ± 0.035	–	38
2 g q6h					
Cefepime [22]					
1 g q8h	Bolus	125 ± 21	0.25 ± 0.04	–	20
1 g q12h					
2 g q8h		143 ± 25	0.23 ± 0.05	–	20
2 g q12h					
Ertapenem [22]					
1 g q12h	0.5-h infusion	29.5 ± 3.4	0.12 ± 0.02	–	95
1 g q24h					
Imipenem [22]					
500 mg q8h	0.5-h infusion	175 ± 23	0.22 ± 0.05	–	8.7
500 mg q6h					
1 g q8h					
1 g q6h					
Meropenem [22]					
500 mg q8h	0.5-h infusion	240 ± 30	0.27 ± 0.04	–	8
500 mg q6h					
1 g q8h					
1 g q6h					
Levofloxacin [22]					
500 mg q24h	1-h infusion	–	–	54.6 ± 11.1	–
Vancomycin [14]					
1 g q12h	1-h infusion	77 ± 22	–	–	–
1 g q8h					
1.5 g q8h					
1.5 g q6h					
2 g q12h					
Daptomycin [15,16]					
4 mg/kg[a] q24h	0.5-h infusion	–	–	494.0 ± 75.0	–
6 mg/kg[a] q24h		–	–	631.8 ± 12.3	–
8 mg/kg[a] q24h		–	–	858.2 ± 24.9	–
10 mg/kg[a] q24h		–	–	1038.8 ± 17.2	–
12 mg/kg[a] q24h		–	–	1277.4 ± 19.8	–
Tigecycline [17]					
50 mg q12h	0.5-h infusion	–	–	6.14 ± 0.76	–
Linezolid [18]					
600 mg q12h	0.5-h infusion	–	–	179.4 ± 62.0	–

CL_t, total body clearance; V_{ss}, apparent volume of distribution at steady-state; AUC_{ss}, area under the antimicrobial concentration–time curve for 24 h; PB, protein binding; q*x*h, every *x* h.

[a] Dose calculated for a standard weight (70 kg).

percentages based on breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have been identified [5]. These divergences have contributed to revising the breakpoints by the CLSI or EUCAST. For instance, the CLSI decreased susceptibility breakpoints of Enterobacteriaceae to cephalosporins [6]. The CLSI also revised the penicillin susceptibility breakpoint for pneumococcal infection outside of the central nervous system and moved it from 0.06 mg/L to 2 mg/L [7].

Breakpoint divergences have been studied less extensively in Gram-positive bacteria, with the exception of glycopeptides [8] or the abovementioned penicillin and pneumococcal infection. The main objective of this study was to compare the susceptibility breakpoints from a PK/PD perspective with the breakpoints defined by the CLSI or EUCAST for Gram-positive bacteria. Detection of divergences in the breakpoints could be useful to explain failures in the treatment of infections by microorganisms considered as susceptible to the antibiotics used to eradicate the infection process.