Comparative antibacterial effects of daptomycin, vancomycin and teicoplanin studied in an in vitro pharmacokinetic model of infection

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Objectives: To compare the antibacterial effects (ABEs) of the free (f) drugs daptomycin, vancomycin and teicoplanin against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant S. aureus (VRSA), using high and low inocula in a pharmacokinetic in vitro model. To determine the daptomycin \( f \)AUC/MIC ratio for a static effect and 3 log reduction in viable count and relate this target to the clinical breakpoint.

Methods: Five clinical MRSA isolates held at Southmead Hospital were used (SMH 15841, SMH 40289, SMH 40275, SMH 33922 and SMH 33024) together with a VRSA isolate (SMH 19898); inocula of \( 10^6 \) and \( 10^8 \) cfu/mL were used. Daptomycin (6 mg/kg once daily), vancomycin (1 g twice daily) and teicoplanin (400 mg once daily) regimens were simulated. ABEs were measured using the 24 h area-under-the-bacterial kill curve (AUBKC) and log change in viable count at 24 h (\( D_{24} \)). For daptomycin, dose escalation was used to determine the relationship between ABE and AUC/MIC.

Results: Daptomycin was bactericidal against the MRSA strains. Daptomycin and vancomycin were active against the VRSA strain; teicoplanin had a static effect. The higher inoculum reduced the ABEs. Analysis of variance (ANOVA) indicated that daptomycin had a superior ABE to teicoplanin and vancomycin. Daptomycin \( f \)AUC/MIC was related to AUBKC and \( D_{24} \); the \( f \)AUC/MIC ratios for a static effect and 1 log and 3 log drop were 37.2 \( \pm \) 16.5, 40.6 \( \pm \) 17.8 and 49.8 \( \pm \) 19.2, respectively.

Conclusions: These data define the \( f \)AUC/MIC sizes for daptomycin for bacteriostatic and bactericidal ABEs and indicate that a 6 mg/kg dose of daptomycin is superior to vancomycin and teicoplanin against MRSA and VRSA strains.

Keywords: MRSA, VRSA, lipopeptides, glycopeptides

Introduction

Increasing antibiotic resistance in Gram-positive pathogens, especially Staphylococcus aureus, represents a major public health challenge. In addition, there has been increasing concern regarding the apparent shift in vancomycin MICs, along with reported cases of clinical failure with apparent vancomycin-susceptible S. aureus strains.\(^1-3\) There have also been published reports of vancomycin failures in patients infected with S. aureus strains with raised population analysis profiles (PAPs) or MICs of 2–4 mg/L.\(^2,3\) Furthermore it has been shown that the time for methicillin-resistant S. aureus (MRSA) bacteraemia clearance was longer for strains with vancomycin MICs of 2 mg/L compared with strains with MICs of \( \leq 1 \) mg/L.\(^4\) Soriano et al.\(^5\) observed that patients with MRSA bacteraemia with a vancomycin MIC >1 mg/L had increased mortality. As there is uncertainty about the likelihood of successful outcomes with vancomycin, newer agents such as daptomycin, a bactericidal, broad-spectrum anti-Gram-positive cyclic lipopeptide antibiotic, have been utilized.

The pharmacodynamics of daptomycin have already been investigated in in vitro pharmacokinetic models and animals.\(^6-8\) However, in these studies the impact of daptomycin’s protein binding was taken into account in non-standard ways. Animal studies have indicated that the AUC/MIC is the main pharmacodynamic index for Streptococcus pneumoniae, S. aureus and Enterococcus spp., as well as identifying \( C_{\text{max}}/\text{MIC} \) as an important contributing pharmacodynamic index.\(^9,10\) Daptomycin’s pharmacokinetics have been studied in both healthy volunteers and patients in Phase 2/3 clinical trials.\(^11-13\) The drug has linear

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Pharmacokinetics up to doses of 6 mg/kg/day, a $t_{1/2}$ of 7–9 h, a volume of distribution of 0.1 L/kg and mainly urinary excretion. Ninety-two percent of the drug is protein bound.

Vancomycin and teicoplanin pharmacokinetics and pharmacodynamics have also been studied in animal and *in vitro* models. AUC/MIC or $T_{\text{MIC}}$ are the dominant pharmacodynamic indices in animals and in *in vitro* systems. In *in vitro* models vancomycin produces a 2–3 log reduction in count at 24 h with standard dose simulations while teicoplanin is bacteriostatic or results in regrowth with some strains of *S. aureus*. The pharmacokinetic variability of all three drugs is partially understood as a result of population pharmacokinetics studied in infected patients. The percentage coefficient of variation (%CV) for total drug clearance (as the main determinant of AUC) is 30% for daptomycin, 26%–38% for vancomycin and 40% for teicoplanin.

One of the objectives of this study was, using free drug concentrations of daptomycin, vancomycin and teicoplanin, to compare their activity in an *in vitro* pharmacokinetic model against typical UKEMRSA-15 and UKEMRSA-16 strains and a vancomycin-resistant *S. aureus* (VRSA) strain with raised daptomycin, vancomycin and teicoplanin MICs. High and low inocula were employed; 10$^{6}$ cfu/mL log phase to compare with typical UKEMRSA-15 and UKEMRSA-16 strains and a flow. The contents of the central chamber were diluted with broth. The central chamber is connected to a collecting vessel for over-night broth culture of *S. aureus* (20% of the total volume). The apparatus, which has been described before, consists of a single central chamber attached to a reservoir containing broth. The apparatus was inoculated into the central chamber to a density of 10$^{8}$ cfu/mL. For experiments with a 10$^{8}$ cfu/mL inoculum, 100 μL of an overnight broth culture of *S. aureus* was inoculated into the central chamber (volume 360 mL) and the model run for 18 h to allow the organism to reach a density of 10$^{8}$ cfu/mL. For experiments with a 10$^{6}$ cfu/mL inoculum, 720 μL of an overnight broth suspension was added to the central chamber and the model run for 45 min. Antibacterials were added to the central chamber and samples were taken from the central chamber throughout the 48 h period at 0, 1, 2, 3, 4, 5, 6, 7, 12, 24, 25, 26, 27, 28, 29, 30, 31, 36 and 48 h for the determination of viable counts. Bacteria were quantified using a Spiral Plater (Don Whitley, Spiral Systems, Shipley, West Yorkshire, UK); the minimum detection level was 10$^{2}$ cfu/mL. Additional aliquots were also stored at −70°C for the measurement of daptomycin, teicoplanin and vancomycin. Daptomycin was assayed by modified bioassay using Penassay Seed Agar; *Bacillus subtilis* was the indicator organism. Teicoplanin and vancomycin were assayed by fluorescence polarized immunoassay (FPIA) methodology (Abbott, Maidenhead, UK and Biostat, Stockport, Cheshire, UK).

**Materials and methods**

**In vitro pharmacokinetic model**

A New Brunswick Bioflo 1000 *in vitro* pharmacokinetic model (Hatfield, Hertfordshire, UK) was used to simulate the free drug serum concentrations associated with daptomycin 6 mg/kg 24 hourly, teicoplanin 400 mg 24 hourly and vancomycin 1000 mg 12 hourly. The apparatus, which has been described before, consists of a single central chamber attached to a reservoir containing broth. The central chamber is connected to a collecting vessel for overflow. The contents of the central chamber were diluted with broth using a peristaltic pump (Ismatec, Cole Palmer, Hanwell, UK) to simulate the drug distribution of the organism to reach a density of 10$^{8}$ cfu/mL. For experiments with a 10$^{8}$ cfu/mL inoculum, 100 μL of an overnight broth culture of *S. aureus* was inoculated into the central chamber (volume 360 mL) and the model run for 18 h to allow the organism to reach a density of 10$^{8}$ cfu/mL. For experiments with a 10$^{6}$ cfu/mL inoculum, 720 μL of an overnight broth suspension was added to the central chamber and the model run for 45 min. Antibacterials were added to the central chamber and samples were taken from the central chamber throughout the 48 h period at 0, 1, 2, 3, 4, 5, 6, 7, 12, 24, 25, 26, 27, 28, 29, 30, 31, 36 and 48 h for the determination of viable counts. Bacteria were quantified using a Spiral Plater (Don Whitley, Spiral Systems, Shipley, West Yorkshire, UK); the minimum detection level was 10$^{2}$ cfu/mL. Additional aliquots were also stored at −70°C for the measurement of daptomycin, teicoplanin and vancomycin. Daptomycin was assayed by modified bioassay using Penassay Seed Agar; *Bacillus subtilis* was the indicator organism. Teicoplanin and vancomycin were assayed by fluorescence polarized immunoassay (FPIA) methodology (Abbott, Maidenhead, UK and Biostat, Stockport, Cheshire, UK).

**Emergence of resistance**

Emergence of resistance was determined by plating aliquots of the bacterial suspension onto nutrient agar plates containing *×2* and *×4* the daptomycin MIC. The risk of emergence of resistance as measured by growth on *×2* MIC and *×4* MIC plates was related to fAUC/MIC.

**Measurement of antibacterial effect and statistical analysis**

The antibacterial effect was assessed by calculating the log change in viable counts between time zero and 24 h (Δ24) and 48 h (Δ48). In addition, the area-under-the-bacterial kill curve (AUBKC; log cfu/mL/h) was calculated by using the log linear trapezoidal rule for the period 0–24 h (AUBKC24) and 0–48 h (AUBKC48). The antibacterial effect measures were compared by analysis of variance (ANOVA) test with the Tukey–Kramer post-test to determine which agents are significantly different from each other. For daptomycin, MICs were determined by modified CLSI methodology using 10% Mueller–Hinton broth with 0.02 or 0.2 mg/L step dilutions.
a sigmoid dose–response variable slope $E_{\text{max}}$ model was used to relate the antibacterial effect measures, i.e. log change in viable count and AUBKC, to AUC/MIC (Graph Pad Prism®).

**Results**

**Pharmacokinetic curves**

The measured daptomycin, teicoplanin and vancomycin concentrations were in good agreement with target concentrations (Figure 1). The %CVs for daptomycin, teicoplanin and vancomycin were 8.6%, 0.45% and 9.9%, respectively.

**MICs**

The daptomycin MICs for the *S. aureus* strains were as follows: SMH 15841, 0.12 mg/L; SMH 40275, 0.06 mg/L; SMH 40289, 0.25 mg/L; SMH 33024, 0.25 mg/L; SMH 33922, 0.19 mg/L; and SMH 19898 (VRSA), 1 mg/L. The teicoplanin and vancomycin MICs were: SMH 15841, 0.25 and 0.38 mg/L; SMH 40275, 1.25 and 0.38 mg/L; SMH 40289, 0.19 and 0.38 mg/L; SMH 33024, 0.25 and 0.19 mg/L; SMH 33922, 0.06 and 0.19 mg/L; and SMH 19898, 16 and 8 mg/L.

**Antibacterial effects**

The antibacterial effects of daptomycin, teicoplanin and vancomycin are shown in Tables 1 and 2 and Figure 2(a–f). Daptomycin demonstrated a superior antibacterial effect to the glycopeptides for both MRSA strains and the VRSA strain. Viable counts were below the limit of detection at 6 h at an inoculum of 10$^6$ cfu/mL and at 24 h at an inoculum of 10$^8$ cfu/mL for strain SMH15841 (Figure 2a and b). Regrowth occurred with strain SMH 33024 with both inocula with initial clearance at

![Figure 1. Target and actual concentrations of daptomycin, vancomycin and teicoplanin.](image)

**Table 1.** Antibacterial effect measures of daptomycin, teicoplanin and vancomycin against three strains of *S. aureus* at an initial inoculum of 10$^6$ cfu/mL.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibacterial effect</th>
<th>log$_{10}$ CFU/mL</th>
<th>log$_{10}$ CFU/mL-h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Δ24</td>
<td>Δ48</td>
</tr>
<tr>
<td>MRSA SMH 15841</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>$-4.3 \pm 0.4^a$</td>
<td>$-4.3 \pm 0.4^a$</td>
<td>5.7 ± 2.8$^b$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>$-1.6 \pm 0.2$</td>
<td>$-1.4 \pm 0.1$</td>
<td>62.3 ± 0.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>$-2.4 \pm 0.5$</td>
<td>$-1.6 \pm 1.3$</td>
<td>41.6 ± 2.2</td>
</tr>
<tr>
<td>MRSA SMH 33024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>$-4.3 \pm 0.2^a$</td>
<td>$-2.2 \pm 1.4$</td>
<td>2.8 ± 0.7$^b$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>$-1.8 \pm 0.6$</td>
<td>$-1.3 \pm 0.9$</td>
<td>68.3 ± 6.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>$-2.7 \pm 0.2$</td>
<td>$-2.8 \pm 0.5$</td>
<td>43.0 ± 1.4</td>
</tr>
<tr>
<td>VRSA SMH 19898</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>$-4.3 \pm 0.1^b$</td>
<td>$-4.3 \pm 0.1^b$</td>
<td>5.5 ± 0.6$^b$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>$+0.3 \pm 0.3$</td>
<td>$+1.8 \pm 0.1$</td>
<td>94.6 ± 3.0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>$-2.9 \pm 0.9$</td>
<td>$-3.8 \pm 0.3$</td>
<td>54.2 ± 8.2</td>
</tr>
</tbody>
</table>

$^a$Daptomycin superior to teicoplanin or vancomycin ($P<0.05$).

$^b$Daptomycin superior to teicoplanin or vancomycin ($P<0.05$); vancomycin superior to teicoplanin ($P<0.05$).
Daptomycin, vancomycin and teicoplanin comparative antibacterial effects

Table 2. Antibacterial effect measures of daptomycin, teicoplanin and vancomycin against three strains of S. aureus at an initial inoculum of $10^8$ cfu/mL.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Antibacterial effect</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log$_{10}$ cfu/mL</td>
<td>log$_{10}$ cfu/mL-h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Delta 24$</td>
<td>$\Delta 48$</td>
<td>AUBKC24</td>
</tr>
<tr>
<td>MRSA SMH 15881</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>-4.8 ± 0.9$^a$</td>
<td>-5.8 ± 0.4$^b$</td>
<td>42.5 ± 6.7$^b$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>-0.6 ± 0.4</td>
<td>-1.9 ± 0.9</td>
<td>136.8 ± 4.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>-2.9 ± 1.0</td>
<td>-3.7 ± 0.9</td>
<td>111.6 ± 28.4</td>
</tr>
<tr>
<td>MRSA SMH 33024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>-5.0 ± 1.6$^a$</td>
<td>-3.9 ± 1.3</td>
<td>43.4 ± 22.0$^b$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>-0.7 ± 0.4</td>
<td>-1.6 ± 0.5</td>
<td>140.4 ± 3.7</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>-2.5 ± 0.3</td>
<td>-3.1 ± 1.0</td>
<td>122.9 ± 5.8</td>
</tr>
<tr>
<td>VRSA SMH 19898</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>-3.1 ± 1.3$^a$</td>
<td>-4.9 ± 0.8$^c$</td>
<td>93.7 ± 21.0$^d$</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>-0.1 ± 0.1</td>
<td>0 ± 0.1</td>
<td>145.7 ± 3.2</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>-1.6 ± 0.3</td>
<td>-3.9 ± 0.6</td>
<td>125.2 ± 3.2</td>
</tr>
</tbody>
</table>

$^a$Daptomycin superior to teicoplanin ($P<0.05$).
$^b$Daptomycin superior to teicoplanin or vancomycin ($P<0.05$).
$^c$Daptomycin or vancomycin superior to teicoplanin ($P<0.05$).
$^d$Daptomycin superior to teicoplanin or vancomycin ($P<0.05$); vancomycin superior to teicoplanin ($P<0.05$).

10$^6$ cfu/mL, but not 10$^8$ cfu/mL (Figure 2c and d). With the VRSA strain SMH 19898 clearance occurred at 10$^6$ cfu/mL, but not 10$^8$ cfu/mL (Figure 2e and f) with daptomycin. At the higher inoculum of 10$^8$ cfu/mL the antibacterial effect as measured by reduction in viable counts at 24 h or the AUBKC indicated that daptomycin had a superior effect compared with teicoplanin and vancomycin (Table 2).

Vancomycin was superior to teicoplanin, producing a 2–3 log reduction in viable count at 24 h against both MRSA strains (Table 1). Against the VRSA strain daptomycin and vancomycin had superior activity to teicoplanin depending on the antibacterial effect measure (Table 2). For vancomycin and teicoplanin, inoculum markedly reduced the antibacterial effect; this was most noticeable with the VRSA strain SMH 19898 where teicoplanin had no effect at an inoculum of 10$^8$ cfu/mL. At 10$^6$ cfu/mL an increase of 1.8 log$_{10}$ in viable count was seen. Antibacterial effect was not affected by daptomycin or vancomycin MIC (4.2–4.5 and 2.4–2.7 log drop, respectively) at $\Delta 24$. MIC did impact on antibacterial effect for teicoplanin; a 1.6–1.8 log drop in viable count was observed with the susceptible strains; no bacterial killing was noted for the strain with an MIC of 16 mg/L at 24 h.

There was good correlation shown when the combined daptomycin fAUC/MIC ratios for the six strains were plotted individually against log change in viable count at 24 h using a sigmoid $E_{max}$ model ($r^2=0.80$). This indicated that a static effect and 1 log and 3 log reduction in count were achieved at ratios of 37.2 ± 16.5, 40.6 ± 17.8 and 49.8 ± 19.2, respectively (Figure 3 and Table 3). A good correlation was also shown between AUC/MIC and AUBKC24 ($r^2=0.78$) (Figure 4). Assessment by growth on $\geq 2$ and $\geq 4$ MIC plates showed that the relative risk of emergence of resistance increased from 17% at AUC/MIC > 40 to 67% ($\times 2$ MIC) or 73% ($\times 4$ MIC) at AUC/MIC ≤ 10 [Table S1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. This correlates well with the fAUC/MICs required for a 1 log drop in viable count.

Discussion

In this study daptomycin was markedly bactericidal against both UK epidemic strains of MRSA and the VRSA strain despite it having a raised daptomycin MIC of 1 mg/L. In general, daptomycin had superior antibacterial effects to vancomycin and teicoplanin in most situations. For all three strains with daptomycin the viable counts were below the limit of detection at 24 h, in contrast to vancomycin and teicoplanin where a maximum 3 log drop in count was noted. Vancomycin had superior activity to teicoplanin noticeably against the VRSA strain.

These results concur with data from a rabbit infective endocarditis model comparing daptomycin (6 mg/kg) with standard (1 g twice daily) and high-dose (1 g four times daily) vancomycin against MRSA and glycopeptide-intermediate S. aureus (GISA) strains with vancomycin MICs of 2 and 8 mg/L and daptomycin MICs of 0.12 and 0.5 mg/L, respectively. Daptomycin was more effective at reducing the bacterial load and sterilized more MRSA vegetations than standard vancomycin therapy. No difference was noted between high and standard vancomycin therapy.$^{23}$

Löwdin et al.$^{24}$ showed similar results to this study using MRSA, methicillin-susceptible S. aureus (MSSA) and methicillin-resistant Staphylococcus epidermidis (daptomycin MICs of 0.5 mg/L) and daptomycin simulations associated with 4 mg/kg; eradication of the in vitro and foreign body model for all
strains occurred by 6–12 h; however, some regrowth occurred at 24 h. Odenholt et al. also observed an inoculum effect in a time–kill curve study using teicoplanin (6 mg/kg) and *S. aureus*. Noticeably less killing was seen as the inoculum increased from 10⁵ to 10⁷ cfu/mL.

Our study results are also similar to those of LaPlante et al. who used free drug concentrations of daptomycin 6 mg/kg and vancomycin (1 g twice daily) in a murine thigh model and an *in vitro* pharmacokinetic model. They compared clindamycin with other antimicrobials against community-acquired MRSA strains with and without inducible clindamycin resistance. Daptomycin and vancomycin MICs ranged from 0.06 to 0.25 mg/L and from 1 to 2 mg/L, respectively, and the inoculum ranged from 10⁵ to 10⁷ cfu/mL. Though increased bacterial killing was seen *in vivo*, daptomycin was bactericidal against all strains at both inocula; a 3–4 log reduction in viable count was observed.

Figure 2. Comparative activity of daptomycin, vancomycin and teicoplanin against: (a) *S. aureus* SMH 15841, 10⁶ inoculum; (b) *S. aureus* SMH 15841, 10⁸ inoculum; (c) *S. aureus* SMH 33024, 10⁶ inoculum; (d) *S. aureus* SMH 33024, 10⁸ inoculum; (e) *S. aureus* SMH 19898, 10⁶ inoculum; and (f) *S. aureus* SMH 19898, 10⁸ inoculum.
in both models. Slight regrowth occurred with two strains after 48 h; in contrast, vancomycin was bacteriostatic at both inocula.

In contrast, Kaatz et al.\(^{26}\) compared daptomycin 8 mg/kg with vancomycin 17.5 mg/kg four times daily, teicoplanin 12.5 mg/kg and high-dose teicoplanin 40 mg/kg against two MSSA, a teicoplanin-resistant MSSA and MRSA in a rabbit endocarditis model. With the exception of the low-dose teicoplanin against the teicoplanin-resistant strain no difference was noted between therapies. Though daptomycin and teicoplanin showed an increase in MIC for one strain the authors concluded that daptomycin and high-dose teicoplanin were as efficacious as vancomycin. These studies used total drug concentrations within their model systems. Clinical data comparing daptomycin with vancomycin plus gentamicin concluded that daptomycin was an effective alternative for MRSA bacteraemia and right-sided endocarditis. Among the patients who received daptomycin and had persistent or relapsed bacteraemia, five patients had isolates with raised daptomycin MICs (≥2 mg/L). In the first human study comparing teicoplanin and vancomycin for the treatment of MRSA endocarditis, no statistically significant difference in hospital mortality rate was seen. The authors concluded that teicoplanin can be an alternative therapy for MRSA infective endocarditis.\(^{27}\)

The pharmacodynamic targets for daptomycin in our study generally correlate well with animal data. Louie et al.\(^{7}\) in a dose–response study using a murine thigh model and S. aureus (ATCC 29213, daptomycin MIC 0.2 mg/L) determined that AUC/MIC was the pharmacodynamic parameter that best correlated to in vivo efficacy. The authors quoted a total AUC/MIC ratio of 245.5 for a static effect; allowing for 92% protein binding this would give an fAUC/MIC of 19.6 compared with 37.2 ± 16.5 in our study. These figures are generally lower than those presented by ourselves and others; however, in this study a single strain and a lower inoculum were used. Saltar et al.\(^{16}\) in a neutropenic murine thigh model using daptomycin total drug concentrations and four strains of S. aureus (daptomycin MICs of 0.5–2 mg/L) calculated AUC/MIC ratios of 388–537, correlating to fAUC/MIC values of 31.04–43.0, respectively, for a static effect, compared with fAUC/MIC ratios of 14.4–63.1 (mean value of 37.2) in our study. These authors also determined that $C_{\text{max}}$/MIC was related to bacterial eradication. This is in agreement with Dandekar et al.\(^{28}\) who, using two strains of MRSA (MICs 0.25 mg/L) in a dose ranging study, also concluded that the AUC/MIC ratio was the best pharmacodynamic predictor of efficacy. Their fAUC/MIC values ranged from 12 to 36 for a bacteriostatic effect to 34 and 110 for an 80% maximum effect (ED\(_90\)). These contrast with data from Akins et al.\(^{29}\), who, using one of the same strains of MRSA and a GISA, reported higher ED\(_90\)/fAUC/MIC values of 1009.7 and 62.2, respectively, in their endocardial vegetation model at a dose of 6 mg/kg ($C_{\text{max}}$ 96–124 mg/L). It was suggested that this discrepancy may be due to a difference in calcium concentrations in the MIC broths.

The current daptomycin EUCAST (‘European Committee on Antimicrobial Susceptibility Testing’)/CLSI breakpoint for staphylococci (≤1 mg/L) is based on a dosing regimen of 4 mg/kg using a mean target AUC/MIC of 438 equating to an fAUC/MIC of 35.30,31 Monte Carlo simulations show that this achieves a 100% target attainment rate (TAR) for strains with an MIC of 0.5 mg/L; in contrast, a TAR of 77.2% is reached for strains with an MIC of 1 mg/L.\(^{32}\) In our study using a 6 mg/kg dose we determined that fAUC/MICs of 37.2 ± 16.5 and 49.8 ± 19.2 were required to produce a static effect and 3 log reduction in viable count. The EUCAST and BSAC surveillance websites show that 20% and 10%, respectively, of MRSA isolates have daptomycin MICs of 1 mg/L.\(^{33}\) In our study using a 6 mg/kg dosing regimen the fAUC/MIC ratios for a static effect varied from 14 to 63, with the total drug AUC for a 6 mg/kg dose at steady state varying between 631 mg.h/L and 747 mg.h/L, equating to fAUCs of 50.48 and 59.76.\(^{11,13}\) These data indicate

### Table 3. Relationship between daptomycin fAUC/MIC and log reduction in count at 24 h

<table>
<thead>
<tr>
<th>Antibacterial effect measure at 24 h</th>
<th>15841</th>
<th>40289</th>
<th>19989</th>
<th>40275</th>
<th>33922</th>
<th>33024</th>
<th>mean data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static effect</td>
<td>52.48</td>
<td>36.3</td>
<td>22.9</td>
<td>63.1</td>
<td>33.9</td>
<td>14.45</td>
<td>37.2 ± 16.5</td>
</tr>
<tr>
<td>1 log drop in viable count</td>
<td>56.23</td>
<td>38.0</td>
<td>23.44</td>
<td>70.79</td>
<td>35.5</td>
<td>19.9</td>
<td>40.6 ± 17.8</td>
</tr>
<tr>
<td>2 log drop in viable count</td>
<td>63.1</td>
<td>42.6</td>
<td>24.0</td>
<td>75.86</td>
<td>38.0</td>
<td>26.3</td>
<td>45.0 ± 18.8</td>
</tr>
<tr>
<td>3 log drop in viable count</td>
<td>74.1</td>
<td>49.0</td>
<td>25.1</td>
<td>75.86</td>
<td>39.8</td>
<td>34.67</td>
<td>49.8 ± 19.2</td>
</tr>
<tr>
<td>EC(_{50})</td>
<td>54.11</td>
<td>39.15</td>
<td>23.68</td>
<td>70.47</td>
<td>37.08</td>
<td>20.26</td>
<td>40.8 ± 17.3</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.9376</td>
<td>0.9845</td>
<td>0.9933</td>
<td>0.9982</td>
<td>0.9583</td>
<td>0.9845</td>
<td></td>
</tr>
</tbody>
</table>

EC\(_{50}\), concentration of a compound where 50% of its maximal effect is observed.
that for these isolates a dosing regimen of 6 mg/kg may be insufficient to obtain a TAR of 100%. This would concur with clinical data where isolates with increased daptomycin MICs (1–2 mg/L) were associated with failure of therapy, often having initially been treated with vancomycin. The emergence of resistance data in this study validate the existing AUC/MIC targets: daptomycin AUC/MICs of >40 are associated with a 1–3 log drop in MRSA bacterial counts and a minimum risk of emergence of resistance. AUC/MICs of <30 are associated with an increased risk of emergence of resistance. For these isolates a dosing regimen of 6 mg/kg may be insufficient to obtain a TAR of 100%.

Our study has shown that daptomycin demonstrates superior bactericidal activity to teicoplanin and vancomycin against UKEMRSA and VRSA strains. Dose ranging experiments indicated that the AUC/MIC associated with a 24 h bacteriostatic to 1 log reduction in count is compatible with a clinical breakpoint of 0.5–1 mg/L.

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Transparency declarations

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Supplementary data

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


Daptomycin, vancomycin and teicoplanin comparative antibacterial effects


