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Pharmacodynamics of Telavancin Studied in an *In Vitro* Pharmacokinetic Model of Infection▽

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The antibacterial effects of telavancin, vancomycin, and teicoplanin against six *Staphylococcus aureus* strains (1 methicillin-susceptible *S. aureus* [MSSA] strain, 4 methicillin-resistant *S. aureus* [MRSA] strains, and 1 vancomycin-intermediate *S. aureus* [VISA] strain) and three *Enterococcus* sp. strains (1 *Enterococcus faecalis* strain, 1 *Enterococcus faecium* strain, and 1 vancomycin-resistant *E. faecium* [VREF] strain) were compared using an *in vitro* pharmacokinetic model of infection. Analyzing the data from all five vancomycin-susceptible *S. aureus* (VSSA) strains or all 4 MRSA strains showed that telavancin was superior in its antibacterial effect as measured by the area under the bacterial kill curve at 24 h ($AUBKC_{24}$) and 48 h ($AUBKC_{48}$) in comparison to vancomycin or teicoplanin ($P < 0.05$). Telavancin was also superior to vancomycin and teicoplanin in terms of its greater early killing effect ($P < 0.05$). Against the three *Enterococcus* spp. tested, telavancin was superior to vancomycin in terms of its $AUBKC_{24}$, $AUBKC_{48}$, and greater early bactericidal effect ($P < 0.05$). Dose-ranging studies were performed to provide free-drug area under the concentration-time curve over 24 h in the steady state divided by the MIC (fAUC/MIC) exposures from 0 to 1,617 (7 to 14 exposures per strain) for 5 VSSA, 4 VISA, and the 3 *Enterococcus* strains. The fAUC/MIC values for a 24-h bacteriostatic effect and a 1-log-unit drop in the viable count were 43.1 ± 38.4 and 50.0 ± 39.0 for VSSA, 3.2 ± 1.3 and 4.3 ± 1.3 for VISA, and 15.1 ± 8.8 and 40.1 ± 29.4 for the *Enterococcus* spp., respectively. The reason for the paradoxically low fAUC/MIC values for VISA strains is unknown. There was emergence of resistance to telavancin in the dose-ranging studies, as indicated by subpopulations able to grow on plates containing 2× MIC telavancin concentrations compared to the preexposure population analysis profiles. Changes in population analysis profiles were less likely with enterococci than with *S. aureus*, and the greatest risk of changed profiles occurred for both species at fAUC/MIC ratios of 1 to 10. Maintaining a fAUC/MIC ratio of >50 reduced the risk of subpopulations able to grow on antibiotic-containing media emerging. These data help explain the clinical effectiveness of telavancin against MRSA and indicate that telavancin may have clinically useful activity against *Enterococcus* spp., and perhaps also VISA, at human doses of 10 mg/kg of body weight/day. In addition, they support a clinical breakpoint of sensitive at ≤1 mg/liter for both *S. aureus* and *Enterococcus* spp.

Telavancin is a semisynthetic lipoglycopeptide with a broad *in vitro* spectrum against Gram-positive human pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) (10, 20). Recent Europe-wide antimicrobial surveillance of clinical Gram-positive isolates indicated that the telavancin MIC_{90} for staphylococci was 0.25 μg/ml, irrespective of methicillin resistance; the MIC_{90} for vancomycin-susceptible enterococci was 0.5 μg/ml; and that for vancomycin-resistant *Enterococcus* strains was 2 μg/ml. *Streptococcus pneumoniae* group A and B beta-hemolytic streptococci and viridans streptococci were all inhibited by ≤0.12 μg/ml telavancin (9). The MIC_{90} against hetero-vancomycin-intermediate *S. aureus* (hVISA) and VISA strains with vancomycin MICs in the range of 4 to 8 μg/ml was 1 μg/ml for telavancin (12).

Telavancin exhibits concentration-dependent killing of methicillin-susceptible *S. aureus* (MSSA), MRSA, and hVISA strains at concentrations 4, 8, and 16 times the MIC, with a postantibiotic effect of 1 to 6 h (20, 21). In vivo experiments in the neutropenic mouse thigh infection model indicated that the free-drug area under the concentration-time curve over 24 h in the steady state/MIC (fAUC/MIC) ratio was most closely related to the antimicrobial effect (8). Experiments in an *in vitro* pharmacokinetic model showed that, using single strains of MSSA and MRSA, the fAUC/MIC ratio for a bacteriostatic effect at 24 h was 40 and that for maximal effect, >3-log-unit kill, it was 400 (19). This contrasts with animal experiments where a fAUC/MIC ratio of 2 to 5 was associated with a 24-h bacteriostatic effect (8). There are as yet no published data on the relationship between the telavancin fAUC/MIC ratio and the antibacterial effect (ABE) against enterococci and no data on the relationship between the fAUC/MIC ratio and the risk of emergence of resistance for *S. aureus* or enterococci.

The aim of this study was to describe the antibacterial effects of telavancin in comparison to those of vancomycin and teicoplanin against *S. aureus* and *Enterococcus* spp. In addition, the relationship between the fAUC/MIC ratio, the antibacterial effect, and the emergence of resistance are established for *S. aureus* and enterococci. A dilution single-compartment in vitro pharmacokinetic model was used.

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TABLE 1. Telavancin, vancomycin, and teicoplanin MICs for *S. aureus* and the *Enterococcus* spp. used

Strain type	Strain no.	MIC (mg/liter)		
		Telavancin	Vancomycin	Teicoplanin
MRSA	22706	0.25	1.5	0.12
MRSA	33024	0.19	0.19	0.25
MRSA	36895	0.19	2.0	0.19
MSSA	38002	0.38	1.5	0.25
MRSA	38601	0.19	1.0	0.19
VISA	19898	0.75	8	16
VISA	24764	1.0		
VISA	25949	1.0		
VISA	26089	0.75		
E. faecalis	37976	0.25	0.75	0.12
E. faecium	37780	0.12	0.25	0.12
E. faecium (VR)	31040	1.5	128	1.5

MATERIALS AND METHODS

In vitro pharmacokinetic model. A New Brunswick Bioflo 1000 in vitro pharmacokinetic model (Hatfield, Hertfordshire, England) was used to simulate free serum concentrations associated with dosages of telavancin, vancomycin, and teicoplanin. The apparatus, which has been described in detail previously, consists of a single central chamber connected to a reservoir containing broth. The central chamber is connected to a chamber collecting overflow (15). The contents of the central chamber were diluted with broth using a peristaltic pump (Ismatec; Bennett & Co., Weston-super-Mare, Somerset, England) at a flow rate of 38.9 ml/h for telavancin, 20 ml/h for teicoplanin, and 47.1 ml/h for vancomycin. The temperature was maintained at 37°C, and the broth in the central chamber was agitated using a magnetic stirrer.

Media. Ten percent Mueller-Hinton broth (MHB) was used in all experiments. Previously, we had shown that 10% broth is able to sustain the growth of *S. aureus* and produced consistent and reproducible results in the model systems (16). Nutrient agar plates (Oxoid, Basingstoke, Hampshire, England) were used to recover *S. aureus* and enterococci from the *in vitro* model. Telavancin was added to the nutrient agar plates in the studies on the emergence of resistance.

Strains. Four strains of MRSA and one strain of MSSA (vancomycin susceptible), four strains of MRSA with reduced vancomycin susceptibility (VISA), and three strains of *Enterococcus* spp. were used. The telavancin, vancomycin, and teicoplanin MICs for the strains are shown in Table 1. The hetero-VISA/VISA phenotype was confirmed by population analysis profiles (27).

Antibiotics. Telavancin was provided by Astellas. Vancomycin and teicoplanin were supplied by Alpharm Ltd., Basingstoke, Hampshire, England. Stock solutions were prepared according to the British Society of Antimicrobial Chemotherapy guidelines (1) and stored at −70°C.

MICs. MICs were determined by the broth dilution method in 10% MHB according to CLSI guidelines (3), except nondoubling dilutions were used to more accurately determine the MIC.

Pharmacokinetics. Telavancin free-drug concentrations in serum associated with a human dose of 10 mg/kg of body weight/24 h were simulated, that is, a target maximum concentration of drug in serum (C_{max}) of 11 mg/liter and a serum half-life ($t_{1/2}$) of 8 h (24). Two doses were simulated over 48 h. In addition, dose-ranging simulations were performed using a $t_{1/2}$ of 8 h and 24-h dosing to achieve a range of AUCs to determine the fAUC/MIC–antibacterial-effect relationship. The free-drug concentrations associated with 1 g intravenous (i.v.) vancomycin given every 12 h were an initial peak of 15 mg/liter and a trough at 12 h of 3.8 mg/liter, with a half-life of 6 h (7, 14). The free-drug concentrations associated with 400 mg i.v. teicoplanin given every 24 h were an initial peak 4.5 mg/liter and a trough at 24 h of 0.75 mg/liter (6). Drug concentrations for telavancin were determined by bioassay using diagnostic sensitivity test (DST) agar and *Bacillus subtilis* as the indicator organism (1). Vancomycin and teicoplanin were assayed by polarization fluoroimmunoassay (Abbott, Berkshire, England).

ABEs. Experiments were performed at an inoculum density of 10^6 CFU/ml; 720 ml of a 10^9-CFU/ml bacterial suspension from a 24-h plate culture was added to the sample chamber 45 min before dosing. Samples were taken throughout the 48-h period for determination of viable counts. Bacteria were quantified using a spiral plater (Don Whitley Spiral Systems, Shiply, Yorkshire, England). The minimum level of detection was 10^2 CFU/ml. Additional aliquots were also stored at −70°C for measurement of the antibiotic concentrations using bioassay and polarization fluoroimmunoassay. All pharmacokinetic simulations of human doses to determine ABE were performed in triplicate.

TABLE 2. Pharmacokinetic parameters for telavancin, vancomycin, and teicoplanin

Parameter[a]	Value		
	Telavancin	Vancomycin	Teicoplanin
C_{max} (mg/liter)	11.1 ± 2.5	13.9 ± 0.2	3.6 ± 0.9
AUC_{0-24} (mg/liter · h)	95.7 ± 3.3	193.4 ± 16.2	43.6 ± 11.2
$t_{1/2}$ (h)	7.4 ± 0.3	5.0 ± 0.4	14.0 ± 6.0
C at 12 h (mg/liter)	2.1 ± 0.5	4.4 ± 1.0	1.6 ± 0.6
C at 24 h (mg/liter)	<1		<1

[a] *C*, concentration.

Emergence of resistance. Resistance to telavancin was assessed as described previously, using population analysis profiles (15) at time zero (preexposure) and at 24 h (postexposure). Samples were placed onto agar containing no antibiotics and antibiotics at 1×, 2×, 4×, and 8× the MIC to quantify any resistant subpopulations. The limit of detection was 10^2 CFU/ml.

Pharmacodynamics and measurement of ABE. The ABEs of the glycopeptides were calculated by determining the log change in viable counts between time zero and 6 h (Δ6), 12 h (Δ12), 24 h (Δ24), 36 h (Δ36), and 48 h (Δ48). The maximum reduction in the viable count was also recorded (Δ max). The time for the inoculum to fall to 99% and 99.9% of its value at time zero was recorded as *T*99 and *T*99.9, respectively. The area under the bacterial kill curve (AUBKC; log CFU/ml · h) was calculated using the log-linear trapezoidal rule for the periods 0 to 24 h ($AUBKC_{24}$) and 0 to 48 h ($AUBKC_{48}$). The relationship between the AUC/MIC ratio and the ABE was delineated using sigmoid Emax models (Graph Pad Prizm; Graph Pad Software Inc., San Diego, CA).

The antibacterial effect measures were compared by analysis of variance (ANOVA) test with the Tukey-Kramer posttest to determine which agents were significantly different from each other.

RESULTS

Pharmacokinetic models. The measured pharmacokinetic parameters for telavancin, vancomycin, and teicoplanin free-drug concentrations are shown in Table 2. Comparisons of the measured antibiotic concentrations and the targeted serum concentration-time profiles were in good agreement (data not shown).

Anti-staphylococcal effect: comparison of telavancin, vancomycin, and teicoplanin at simulated human doses. A series of simulations were performed to compare the antibacterial effect of telavancin to those of vancomycin and teicoplanin versus five strains of vancomycin-susceptible *S. aureus* (four MRSA strains plus one MSSA strain). The $AUBKC_{24}$ and $AUBKC_{48}$ were taken as the coprimary endpoints to compare the activity of telavancin to those of vancomycin and teicoplanin. For the three MRSA strains (33024, 36895, and 38601) with telavancin MICs of 0.19 μg/ml, telavancin was superior to both vancomycin and teicoplanin at 24 h and 48 h (ANOVA, $P < 0.05$). For MRSA strain 27706 (telavancin MIC, 0.25 μg/ml) and the MSSA strain (MIC, 0.38 μg/ml), no differences were detected between the strains in terms of antibacterial effects. Against VISA strain 19898 (telavancin MIC, 0.75 μg/ml), telavancin and vancomycin were superior to teicoplanin (ANOVA, $P < 0.05$). In analysis of the secondary endpoints, telavancin was superior to teicoplanin as measured by the log drop in the viable count at 6 h for MRSA strains 33024 and 38601, and telavancin was superior to vancomycin and teicoplanin for strain 33024. Against VISA strain 19898, telavancin was supe-

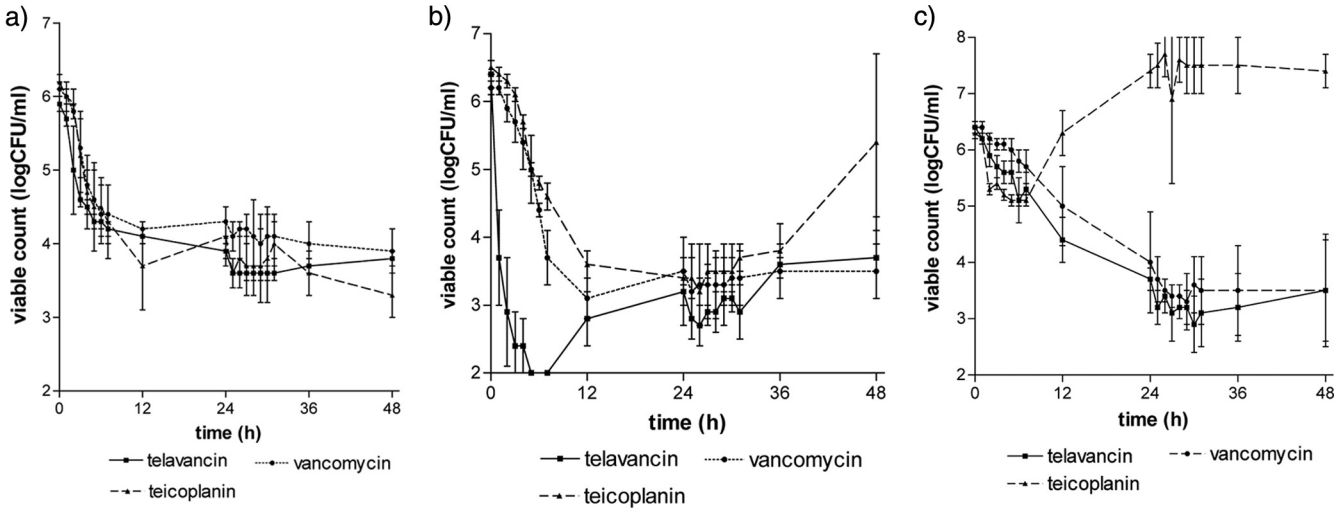

FIG. 1. Antibacterial effect of simulated human free-drug serum concentration-time profiles of telavancin, vancomycin, and teicoplanin against MSSA strain 38002 (a), MRSA strain 36895 (b), and VISA strain 19898 (c). The error bars indicate standard deviations.

rior to vancomycin in terms of the log reduction in the viable count at 6 h. For the log drop in the viable count at 12 h, telavancin was superior to vancomycin and teicoplanin for MRSA strains 33024 and 38601 (ANOVA, $P < 0.05$).

The relative antibacterial effects of telavancin, vancomycin, and teicoplanin against MSSA, MRSA strain 36895, and a VISA strain are shown in Fig. 1, and the comparable activities of the drugs against the four MRSA strains are summarized in Table 3. Telavancin was superior to vancomycin and teicoplanin against MRSA strains in terms of the log reduction in viable counts at 6 h and 12 h; the maximum reduction in the count; and the coprimary measures of antibacterial effect, $AUBKC_{24}$ and $AUBKC_{48}$.

All three glycopeptides had poorer activity against the VISA strain in terms of $AUBKC_{24}$ than the five vancomycin-susceptible strains: for telavancin, the AUBKC of the VISA strain was 55.1 ± 4.8 mg/liter/h and the AUBKC of five vancomycin-susceptible *S. aureus* strains was 26.0 ± 14.3 mg/liter · h ($P < 0.05$). The vancomycin AUBKC for the VISA strain was 65.6 ± 10.8; and the AUBKC for vancomycin-susceptible *S. aureus* was 40.3 ± 15 ($P < 0.05$). The teicoplanin AUBKC for the VISA strain was 92.8 ± 5.0; the AUBKC for vancomycin-susceptible *S. aureus* was 44.3 ± 7.0 ($P < 0.05$).

TABLE 3. Comparative antibacterial effects of free-drug serum concentrations of simulations of telavancin, teicoplanin, and vancomycin against pooled data from 4 MRSA strains

ABE measure	Value		
	Telavancin	Teicoplanin	Vancomycin
No. of simulations	18	12	17
Log change in viable count (log CFU/ml) at (h):			
6	−3.5 ± 0.6[a]	−2.0 ± 0.4	−2.5 ± 0.7
12	−3.5 ± 0.5[a]	−2.7 ± 0.2	−3.0 ± 0.7
24	−3.0 ± 0.8	−2.8 ± 0.5	−2.8 ± 0.8
36	−3.0 ± 0.7	−2.7 ± 0.8	−2.7 ± 0.9
48	−2.8 ± 0.8	−2.1 ± 1.4	−2.8 ± 1.0
Maximum reduction in viable count (log CFU/ml)	−4.0 ± 0.5[a]	−3.2 ± 0.5	−3.3 ± 0.6
$AUBKC_{24}$ (log CFU/ml · h)	21.7 ± 7.7[a]	42.0 ± 5.3	36.9 ± 13.7
$AUBKC_{48}$ (log CFU/ml · h)	43.8 ± 20.0[a]	76.3 ± 21.1	65.9 ± 29.4

[a] Telavancin was superior to vancomycin and teicoplanin ($P < 0.05$).

Antienterococcal effect: comparison of telavancin, vancomycin, and teicoplanin at simulated human doses. A second series of experiments were performed to compare the antibacterial effects of telavancin, vancomycin, and teicoplanin against three strains of *Enterococcus* spp.: vancomycin-susceptible *Enterococcus faecalis* (strain 37976), vancomycin-susceptible *Enterococcus faecium* (strain 37780), and vancomycin-resistant *E. faecium* (strain 31040).

In terms of the coprimary antibacterial effect measures, $AUBKC_{24}$ and $AUBKC_{48}$, telavancin was superior to vancomycin and teicoplanin against all three strains. The $AUBKC_{24}$ for telavancin against strain 37976 (*E. faecalis*) was 59.9 ± 3.0, and the corresponding values were 74.7 ± 4.1 for vancomycin and 74.6 ± 4.2 for teicoplanin (ANOVA, $P < 0.05$). The $AUBKC_{48}$ for telavancin against strain 37976 was 101.0 ± 1.3, that for vancomycin was 135.4 ± 12.8, and that for teicoplanin was 137.6 ± 3.4 (ANOVA, $P < 0.05$). The $AUBKC_{24}$ for telavancin against strain 37780 (*E. faecium*) was 67.3 ± 1.0, and the corresponding values were 76.2 ± 2.8 for vancomycin and 80.3 ± 3.9 for teicoplanin (ANOVA, $P < 0.05$). The $AUBKC_{48}$ for telavancin against strain 37780 was 113.5 ± 3.9, that for vancomycin was 125.0 ± 3.9, and that for teicoplanin was 146.5 ± 9.9 (ANOVA, $P < 0.05$). The $AUBKC_{24}$ for telavancin against strain 31040 (vancomycin-resistant *E. faecium*) was 72.1 ± 3.2, and the corresponding values were 126.8 ± 1.8 for vancomycin and 121.2 ± 1.9 for teicoplanin (ANOVA, $P < 0.05$). The $AUBKC_{48}$ for telavancin against strain 31040 was 137.6 ± 7.1, that for vancomycin was 262.3 ± 5.9, and that for teicoplanin was 242.1 ± 3.4 (ANOVA, $P < 0.05$). In terms of the log drop

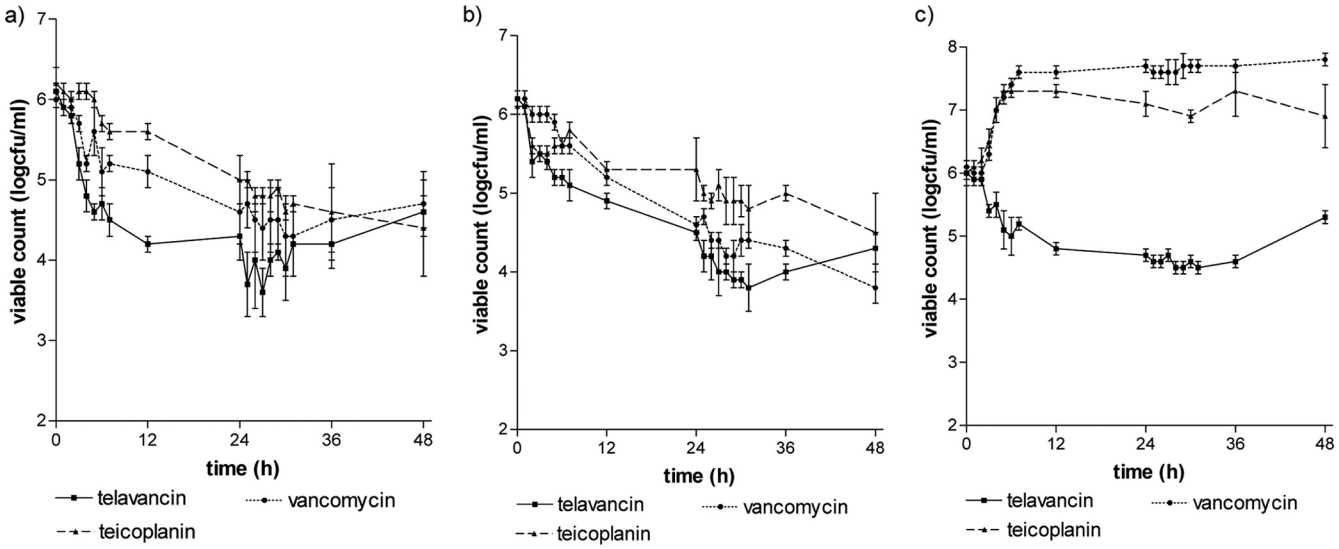

FIG. 2. Antibacterial effect of simulated human free-drug serum concentration-time profiles of telavancin, vancomycin, and teicoplanin against *E. faecalis* strain 37976 (a), *E. faecium* strain 37780 (b), and vancomycin-resistant *E. faecium* strain 31040 (c). The error bars indicate standard deviations.

in the viable count at 6 h and 12 h, telavancin also had a superior antibacterial effect against all three strains compared to either vancomycin or teicoplanin (ANOVA, $P < 0.05$) (Fig. 2).

Dose-ranging *S. aureus*. A range of doses ($n = 7$ to 12) per strain were used to provide fAUC/MIC ratios from 0 to 510. The antibacterial effect was measured by the Δ24 and $AUBKC_{24}$ for each strain. The Δ24 was related to the fAUC/MIC ratio using a sigmoid Emax model (Table 4 and Fig. 3). Using the Δ24 as the primary antibacterial-effect measure, the fAUC/MIC ratio for vancomycin-susceptible *S. aureus* for static effect was 43.1 ± 38.4, the −1-log-unit reduction in the viable count was 50.0 ± 39.0, and the −2-log-unit reduction in the count was 55.1 ± 37.2 (Table 4). The 90% maximum antibacterial effect, as measured by the $AUBKC_{24}$, occurred at fAUC/MIC ratios of >40 (Fig. 3) for vancomycin-susceptible *S. aureus*. There was marked strain-to-strain variability in the fAUC/MIC ratio for the 24-h static effect, with a range from 3.1 to 95.0 among the 5 strains tested. Among the MRSA strains ($n = 4$), the range in fAUC/MIC ratios for the static effect was 11.8 to 95.0 (mean ± standard deviation [SD], 53.1 ± 36.1). In contrast to the four VISA strains, the fAUC/MIC ratio for the 24-h static effect was 3.2 ± 1.3 (range, 2.1 to 4.8); the −1-log-unit reduction in the count was 4.3 ± 1.3, and the −2-log-unit reduction in the count was 6.0 ± 1.1 (Table 4).

Dose-ranging: enterococci. A range of doses ($n = 9$ to 14) per strain were used to provide fAUC/MIC ratios up to 1,617. The antibacterial effect was measured, as for *S. aureus*, by the Δ24 and $AUBKC_{24}$ and related to the fAUC/MIC ratio in a sigmoid Emax model (Table 4 and Fig. 3). Employing the Δ24, the fAUC/MIC ratio for a 24-h static effect ranged from 5.6 to 22.9 (mean, 15.1). The 90% maximum antibacterial effect, as measured by the $AUBKC_{24}$, occurred at a fAUC/MIC ratio of >70 (Fig. 3).

Emergence of resistance to telavancin. With the 10-mg/kg/24 h dose simulations, no emergence of resistance occurred, as measured by changes in population analysis profiles over 48 h, with either *S. aureus* or *Enterococcus* spp. Changes in population profiles for *S. aureus* were related to the fAUC/MIC ratio and occurred in 100% of the experiments where the fAUC/MIC ratio was in the range from >1 to 10 but in none of the

TABLE 4. Relationship between telavancin free-drug AUC/MIC ratio and antibacterial effect at 24 h for vancomycin-susceptible *S. aureus*, vancomycin-intermediate *S. aureus*, and *Enterococcus* spp.

Strain	Telavancin MIC (μg/ml)	fAUC/MIC ratio		
		Static effect	−1-log-unit reduction in viable count	−2-log-unit reduction in viable count
MRSA				
33024	0.19	95.0	98.4	105.5
36895	0.19	67.7	80.4	95.5
38601	0.19	37.8	43.3	
27706	0.25	11.8	23.5	49.6
38002	0.38	3.1	4.4	15.8
Mean ± SD		43.1 ± 38.4	50.0 ± 39.0	55.1 ± 37.2
VISA				
19898	0.75	2.1	3.1	4.7
26089	0.75	4.8	6.1	7.4
24764	1.0	2.3	3.6	5.9
25949	1.0	3.7	4.7	6.0
Mean ± SD		3.2 ± 1.3	4.3 ± 1.3	6.0 ± 1.1
E. faecium 37780	0.12	17.0	60.2	
E. faecalis 37976	0.25	5.6	6.3	
VR *E. faecium* 31040	1.5	22.9	53.7	170
Mean ± SD		15.1 ± 8.8	40.1 ± 29.4	

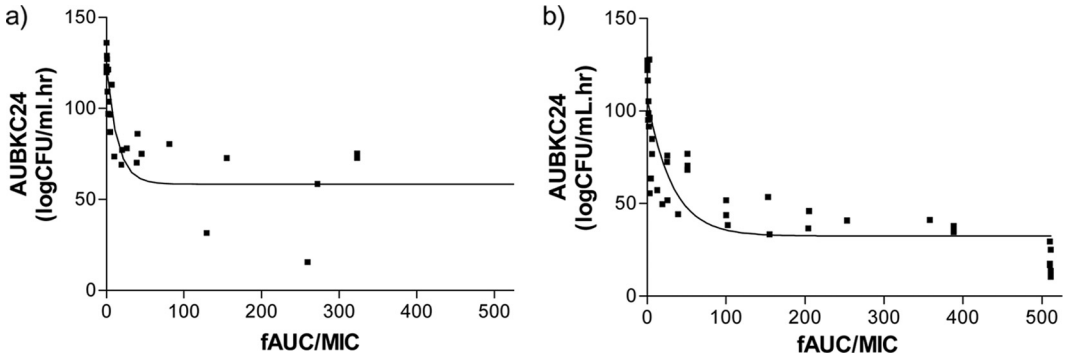

FIG. 3. Telavancin fAUC/MIC relationship $AUBKC_{24}$ for vancomycin-susceptible *S. aureus* (a) and *Enterococcus* spp. (b).

experiments where the fAUC/MIC ratio was >400 (Table 5). The number of CFU able to grow on culture plates containing telavancin at 2× the MIC was also related to the fAUC/MIC ratio and was highest at values of >1 to 3 and lowest at fAUC/MIC ratios of >400 (Table 5). With enterococci, the risk of changes in the telavancin population profile was greatest at fAUC/MIC ratios of >3 to 10 (Table 5), and the overall risk of emergence of resistance with enterococci was less than with *S. aureus*, occurring in 6/33 experiments with enterococci compared to 18/38 with *S. aureus*.

DISCUSSION

Telavancin at humanized drug exposures has been shown to be as effective as humanized doses of vancomycin against MRSA in a rabbit endocarditis model and superior to vancomycin in MRSA infection in murine pneumonia and bacteremia models (17, 22, 23). In an *in vitro* pharmacokinetic endocarditis model, total serum concentrations of telavancin associated with 10-mg/kg/24 h doses were superior in their effects to those associated with 1-g/12 h vancomycin doses against an MSSA strain, but not an MRSA strain (11). Our data help explain these discrepant findings by showing that different MRSA or *S. aureus* strains vary in their responses to humanized exposures of telavancin and vancomycin, so that for most, but not all, strains telavancin has a antibacterial effect superior to that of vancomycin. Our analysis of all our MRSA data (4 strains) and all the data on vancomycin-susceptible *S. aureus* strains (5 strains) indicates a clear superiority of telavancin over vancomycin in terms of early bactericidal action (up to 12 h), as well as the total antibacterial effect over 24 or 48 h. There are no published preclinical data comparing the antibacterial effects of telavancin and teicoplanin against *S. aureus*. As with vancomycin, telavancin shows superiority to teicoplanin for the majority of individual strains tested and also in the analysis of all *S. aureus* strains together. A clearer picture is emerging from preclinical models in terms of telavancin activity against hVISA and VISA strains. Telavancin has been shown to be more bactericidal than vancomycin against hVISA and VISA strains in a rabbit endocarditis model (17, 18). In addition, simulation of total drug serum concentrations of telavancin and vancomycin modeled in an *in vitro* endocarditis system again showed superiority of telavancin over vancomycin against hVISA and VISA (11). Our data employing a single VISA strain indicate telavancin is superior to vancomycin in terms of its early bactericidal activity and superior to teicoplanin over 24 or 48 h. Teicoplanin's antibactericidal effect against the VISA strain was noticeably poor.

There are no published data on the comparative activities of telavancin, vancomycin, and teicoplanin against enterococcal species. Against the vancomycin-susceptible *E. faecalis* and *E. faecium* strains we tested, telavancin was superior to vancomycin and teicoplanin in terms of its early bactericidal activity up to 12 h and also its overall antibacterial effect up to 24 or 48 h. Telavancin also had a noticeably greater antibacterial effect against vancomycin-resistant *Enterococcus* spp. (VRE) than either vancomycin or teicoplanin. However, the strain we used had a telavancin MIC of 1.5 μg/ml, and VRE strains have telavancin MICs up to 8 μg/ml, with MIC_{50} values of 2 to 4

TABLE 5. Relationship between telavancin free-drug AUC/MIC ratio and risk of emergence of resistance in vancomycin-susceptible *S. aureus* and *Enterococcus* sp. strains as assessed by organism growth on 2× MIC recovery media

fAUC/MIC ratio	*S. aureus*			*Enterococcus* spp.		
	No. of expt	% with growth on 2× MIC recovery media (*n*)	Viable count (log CFU/ml) on 2× MIC recovery plates	No. of expt	% with growth on 2× MIC recovery media (*n*)	Viable count (log CFU/ml) on 2× MIC recovery plates
<1	0			3	0	<2
≥1–3	8	100 (8)	5.6 ± 1.9	7	29 (2)	3.6
>3–10	3	100 (3)	4.7 ± 0.6	5	60 (3)	3.1 ± 0.9
>10–50	8	50 (4)	4.3 ± 1.1	6	17 (1)	4.4
>50–175	7	29 (2)	4.2	3	0	<2
>175–400	7	14 (1)	2.1	4	0	<2
>400	5	0	<2	5	0	<2

μg/ml (9, 10); hence, this strain, though typical of VRE, does not have an especially high telavancin MIC.

The sizes of the total drug AUC/MIC ratio associated with a 24-h static or −1-log-unit reduction in viable counts of *S. aureus* in a neutropenic mouse thigh infection model were 70 to 90 and 300 to 350, respectively (8). The 24-h static dose/MIC ratio varied by 10-fold across the 8 strains of *S. aureus* tested, indicating considerable strain-to-strain variation. In contrast to these data, Odenholt et al. (19), using an *in vitro* pharmacokinetic model but only a single *S. aureus* strain, reported that a free-drug AUC/MIC ratio of 50 produced a 24-h bacteriostatic effect, while a fAUC/MIC ratio of 400 was required for maximum effect. Our data are more in keeping with those of Odenholt in that a free-drug AUC/MIC ratio of 43.1 ± 38.4 was needed to produce a 24-h bacteriostatic effect, a ratio of 50.0 ± 39.0 was needed for a −1-log-unit reduction in the viable count, and a ratio of >150 was associated with a maximum effect against vancomycin-susceptible *S. aureus* strains. Among our 5 *S. aureus* strains, there was a 30-fold between-strain variation in the fAUC/MIC ratio required for static effect; this is greater than the 5-fold variation we noted with daptomycin and the 12-fold variation with tomopenem (2, 16) when tested with *S. aureus*. The fAUC/MIC ratio for antibacterial effect of telavancin on VISA strains has not been previously reported. Our data indicate that the fAUC/MIC ratios for static and −1-log-unit reductions in viable counts of VISA strains are 10- to 20-fold lower than with vancomycin-susceptible *S. aureus* (VSSA) strains. The reason for this finding is unclear and may be artifactual, related to a greater number of VISA strains being required to produce a single CFU on recovery media. This in turn could be related to a greater propensity for VISA strains to clump compared to VSSA strains as a result of cell wall changes. Results similar to ours have been reported previously, comparing the activities of vancomycin against VISA and VSSA. Turner et al. (26) showed that the vancomycin-nonsusceptible subpopulation of VISA strains was more rapidly eradicated from an *in vitro* pharmacokinetic model than the susceptible population after exposure to vancomycin using simulated human pharmacokinetics. A decade ago, Dudley et al. (5) reported that lower vancomycin AUC/MIC ratios were required for VISA than VSSA strains to produce a 50% maximum kill or a maximum kill in a neutropenic murine thigh model. More recently, Craig and Andes (4) showed that the vancomycin fAUC/MIC ratios for −2-log-unit kill with VISA were 28 to 40 but that they were 138 to 263 for other *S. aureus* strains.

The maximum risk of emergence of resistance to telavancin was at fAUC/MIC ratios below the 24-h static-effect size. With VSSA strains, a resistant subpopulation was recovered in 100% (11/11) of experiments performed, with fAUC/MIC ratios of 1 to 10. The resultant subpopulations were less likely to be detected with *Enterococcus* spp., occurring in 42% (5/12) of experiments. Previously, we described similar data with *S. aureus* strains exposed to tomopenem or daptomycin, that is, the maximum risk of resistance and its maximum amplification occur below the 24-h bacteriostatic-effect size of the dominant pharmacodynamic index. However, there is also a smaller but quantifiable risk at the pharmacodynamic index size associated with a 24-h bacteriostatic effect or −1-log-unit kill (2, 16).

The total AUC_{24} (mg/liter · h) when 10 mg/kg/day telavancin was administered to healthy volunteers was 762 ± 81 mg/liter · h; however, as protein binding is about 90%, a free-drug AUC_{24} of about 50 to 100 mg/liter · h may be expected in infected patients (13, 24). Given a fAUC/MIC target of 40 to 50 for VSSA and 25 to 50 for enterococci, our data would support a clinical breakpoint for these species of ≤1 mg/liter telavancin. This indicates that VSSA and VSE strains should respond clinically to 10 mg/kg/day telavancin and is supported by the clinical-trial evidence so far published for VSSA (25). There are no clinical data on telavancin's effectiveness against hVISA or VISA strains, but our findings of a low fAUC/MIC ratio to produce a 24-h bacteriostatic effect, together with other preclinical model data, are supportive of the potential to use telavancin to treat such strains.

In conclusion, the pharmacokinetic infection model data indicate telavancin is likely to have a clinically useful antibacterial effect in therapy of VSSA, VISA, and enterococcal infections in humans. Telavancin had an antibacterial effect superior to those of vancomycin and teicoplanin against most strains of MRSA and enterococci, while a fAUC/MIC ratio of 40 to 50 was associated with a 24-h bacteriostatic to −1-log-unit kill of VSSA and enterococci. A paradoxically low fAUC/MIC ratio of 2 to 6 for VISA strains suggests telavancin may have useful activity against these still rare pathogens. The emergence of resistance risk can be minimized by keeping the telavancin fAUC/MIC ratio >50 for both *S. aureus* and enterococci.

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