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Comparative Efficacies of Tedizolid Phosphate, Vancomycin, and Daptomycin in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* Endocarditis

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Tedizolid, the active component of the prodrug tedizolid phosphate, is a novel oxazolidinone that is approximately 4 times more active by weight than linezolid against *Staphylococcus aureus in vitro*. The *in vivo* efficacy of tedizolid phosphate (15 mg/kg body weight intravenous [i.v.] twice a day [b.i.d.]) was compared to those of vancomycin (30 mg/kg i.v. b.i.d.) and daptomycin (18 mg/kg i.v. once a day [q.d.]) in a rabbit model of aortic valve endocarditis (AVE) caused by methicillin-resistant *S. aureus* strain COL (infection inoculum of 10^7 CFU). Median vegetation titers of daptomycin-treated rabbits were significantly lower than those of rabbits treated with tedizolid phosphate (15 mg/kg b.i.d.) ($P = 0.016$), whereas titers for vancomycin-treated compared to tedizolid-treated rabbits were not different ($P = 0.984$). The numbers of organisms in spleen and kidney tissues were similar for all treatment groups. A dose-ranging experiment was performed with tedizolid phosphate (2, 4, and 8 mg/kg b.i.d.) compared to vancomycin (30 mg/kg b.i.d.), using a higher infecting inoculum (10^8 CFU) to determine the lowest efficacious dose of tedizolid phosphate. Tedizolid phosphate (2 mg/kg) (equivalent to 60% of the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) for the human 200-mg dose approved by the U.S. Food and Drug Administration) was not efficacious. Tedizolid phosphate at 4 mg/kg (equivalent to 75% of the AUC_{0-24} for the human 400-mg dose) and 8 mg/kg produced lower vegetation titers than the control, but neither was as efficacious as vancomycin.

Staphylococcus aureus is a common cause of skin and soft tissue infections and invasive disease, such as bacteremia and endocarditis. Tedizolid, the microbiologically active moiety of the prodrug tedizolid phosphate (TZD), is a novel oxazolidinone approved for treatment of acute bacterial skin and skin structure infections caused by Gram-positive bacteria, including strains of methicillin-resistant *S. aureus* (MRSA). Tedizolid phosphate is rapidly cleaved in the bloodstream to yield the active component, tedizolid. It is approximately 4 times more active by weight than linezolid against *S. aureus in vitro* (1) and 16 times more active against *cfr* plasmid carrying linezolid-resistant staphylococci *in vitro* (2). Moreover, unlike the bacteriostatic activity of linezolid, tedizolid has been shown to have some bactericidal activity in a neutropenic mouse thigh model (3, 4). To assess further its potency and bactericidal activity *in vivo*, tedizolid was compared to vancomycin and daptomycin in a rabbit model of aortic valve endocarditis (AVE) caused by the MRSA strain COL.

MATERIALS AND METHODS

Bacterial strains. *S. aureus* strain COL is a homogeneous, methicillin-resistant strain. COL inoculum was prepared by diluting a frozen stock in 0.9% injectable sodium chloride. The frozen stock was prepared from an overnight culture grown in tryptic soy broth. Cells were washed and resuspended in phosphate-buffered saline with 10% glycerol and stored at −80°C.

Susceptibility studies. Susceptibility studies were performed by broth dilution to determine the MICs using standard CLSI methods (5). Briefly, the bacteria and drugs were diluted in cation-adjusted Mueller-Hinton broth (CAMHB) and incubated at 37°C overnight. Ca^{2+} supplementation was provided for daptomycin testing (6). The MIC was determined as the lowest concentration of drug that inhibited growth. Tedizolid and daptomycin standard powder for *in vitro* testing were provided by the manufacturers, and vancomycin was purchased from Sigma-Aldrich.

Time-kill studies. Time-kill studies were conducted in duplicate at 37°C in 10 ml of CAMHB containing vancomycin at 5 μg/ml (5× MIC), daptomycin at 5 μg/ml (5× MIC), or tedizolid at 2 μg/ml (16× MIC) at a starting inoculum of 10^6 CFU/ml.

Rabbit model of endocarditis. New Zealand White rabbits (2.5 to 3 kg) were used. Endocarditis was established by standard methods (7). Briefly, a cutdown was made over the right carotid artery. A polyethylene catheter was introduced via carotid arteriotomy, positioned into the left ventricle, and sutured in place. Forty-eight hours later, a 1-ml suspension of 10^7 to 10^8 CFU of *S. aureus* in 0.9% NaCl was injected intravenously (i.v.). On postinoculation day 1, approximately 16 to 18 h after infection, untreated control rabbits were sacrificed to determine pretreatment bacterial counts. The hearts, spleens, and kidneys were harvested. Aortic valves and endocardial vegetations and approximately 0.2-g samples of spleen and kidney were placed in 1.0 ml of 0.9% NaCl and homogenized with a tissue grinder. Ten-fold serial dilutions of homogenate were prepared, and 0.1-ml volumes were inoculated onto blood agar medium, which was incubated for 24 to 48 h at 37°C. The numbers of CFU were counted to determine the tissue burdens of organisms. The lower limit of detection is approximately 2 $\log_{10}$ CFU/g.

Antibiotic-treated rabbits were administered 15, 8, 4, or 2 mg/kg tedi-

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zolid phosphate (Trius Pharmaceuticals) i.v. twice a day (b.i.d.) for 4 days, 30 mg/kg vancomycin (APP Pharmaceuticals, LLC., Schaumburg, IL) i.v. b.i.d. for 4 days, or 18 mg/kg daptomycin (Cubist Pharmaceuticals) i.v. once a day (q.d.) for 4 days. The vancomycin and daptomycin concentrations used for rabbit dosing were chosen to simulate similar pharmacokinetic and pharmacodynamic values achieved with recommended dosing in humans (8–10). The first dose of drug was administered 18 to 20 h after inoculation.

Treated rabbits were sacrificed on postinoculation day 5 approximately 18 to 24 h after the last dose of daptomycin and 12 to 18 h after the last dose of vancomycin and tedizolid phosphate. Bacterial burdens in endocardial vegetations, spleens, and kidneys were determined as described above for controls. Rabbits that died prior to sacrifice on day 5 or those sacrificed because of moribund condition had quantitative tissue cultures performed and were included in the data analysis only if they had received at least 24 h of therapy. Animals were maintained in accordance with the American Association for Accreditation of Laboratory Animal Care criteria. The Animal Research Committee (IACUC) of the University of California, San Francisco, approved these animal studies.

Plasma tedizolid concentrations. Blood was obtained on day 2 1 h and 9 h after i.v. injection of tedizolid phosphate and again during sacrifice at 18 h posttreatment for determination of serum drug concentrations, which were assayed by high-performance liquid chromatography (HPLC). Samples were collected in heparinized syringes and centrifuged at 4°C, and plasma was isolated and stored at −80°C. Pharmacokinetic assays were performed by the manufacturer. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule, assuming first-order kinetics.

Protein binding of tedizolid in New Zealand White rabbits was performed by the manufacturer as previously described (11). Briefly, K_2EDTA-plasma from rabbits was evaluated by high-throughput dialysis. Tedizolid was spiked into rabbit plasma to final concentrations of 1 and 10 μg/ml and dialyzed at 37°C for 6 h.

Statistical analysis. The number of organisms in tissues was expressed as $\log_{10}$ colony-forming units per gram. Tissue samples with no growth were assigned a value of the lower limit of detection calculated as $\log_{10}$ (10 CFU/weight of tissue sample in grams). Median values and interquartile differences were calculated for each group. *P* values for differences in bacterial burden in tissues between groups were determined by the Mann-Whitney U test uncorrected for multiple comparisons. Differences for which *P* values were >0.05 were considered not to be statistically significant.

RESULTS

The MICs of tedizolid, vancomycin, and daptomycin against the COL strain were 0.125, 1, and 1 μg/ml, respectively. Tedizolid achieved a 0.69-$\log_{10}$-CFU/ml reduction of the starting inoculum after 24 h in time-kill studies, compared to reductions of 2.8 $\log_{10}$ CFU/ml for vancomycin and 3.1 $\log_{10}$ CFU/ml for daptomycin (Fig. 1).

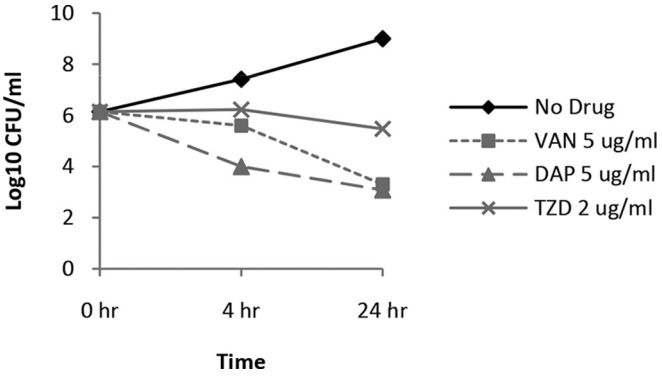

FIG 1 Comparative time-kill studies for vancomycin (VAN), daptomycin (DAP), and tedizolid (TZD) against MRSA strain COL.

Comparative study of tedizolid at 15 mg/kg i.v. b.i.d., vancomycin at 30 mg/kg i.v. b.i.d., and daptomycin at 18 mg/kg i.v. q.d. at an inoculum of 10^7 CFU. Fifty-three rabbits were included in this study. Two rabbits randomized to the vancomycin group died before 24 h of treatment and were thus excluded from data analysis. Two additional deaths occurred during treatment—one from the vancomycin group on day 2 of therapy and the other from the daptomycin group on day 3 of therapy. Eight untreated control rabbits and 15 tedizolid phosphate-treated, 14 daptomycin-treated, and 14 vancomycin-treated rabbits were included in this study.

The burden of organisms in vegetations was lower in the tedizolid phosphate-treated rabbits than that in the no-treatment control, with a median 1.5-$\log_{10}$-CFU/g decrease in titer ($P = 0.026$) (Table 1). There was no difference between tedizolid phosphate- and vancomycin-treated rabbits, with median titers of 6.4 and 5.5 $\log_{10}$ CFU/g in vegetations at the end of therapy, respectively. The median vegetation titer for daptomycin-treated rabbits was 2.7 $\log_{10}$ CFU/g (5.2 $\log_{10}$ CFU/g lower than that in untreated controls) and significantly lower than that achieved with tedizolid phosphate ($P = 0.016$).

The burden of organisms in the spleen was significantly lower in the tedizolid phosphate-treated rabbits than in the no-treatment control, with a 1.7-$\log_{10}$-CFU/g decrease ($P = 0.006$). Results for tedizolid phosphate-treated rabbits were similar to those for vancomycin- and daptomycin-treated rabbits, with median organism titers of tedizolid phosphate, daptomycin, and vancomycin of 3.0, 1.8, and 2.7 $\log_{10}$ CFU/g, respectively. The burden of organisms in the kidneys was similar in tedizolid phosphate-

TABLE 1 Comparative study of tedizolid phosphate, daptomycin, and vancomycin

Treatment (no. of rabbits)	Median organism titer, $\log_{10}$ CFU/g (IQD)[a]			*P* value vs:					
				Control			Tedizolid phosphate		
	Vegetation	Spleen	Kidney	Vegetation	Spleen	Kidney	Vegetation	Spleen	Kidney
Control (8)	7.9 (2.2)	4.7 (1.3)	3.4 (2.8)	Ref[b]	Ref	Ref	0.026	0.006	0.057
Tedizolid phosphate, 15 mg/kg i.v. b.i.d. (15)	6.4 (3.4)	3.0 (2.5)	2.3 (1.3)	0.026	0.006	0.057	Ref	Ref	Ref
Daptomycin, 18 mg/kg i.v. q.d. (14)	2.7 (1.4)	1.8 (0.2)	1.7 (0.2)	0.002	<0.001	0.002	0.016	0.430	0.112
Vancomycin, 30 mg/kg i.v. b.i.d. (14)	5.5 (3.9)	2.7 (3.8)	2.0 (1.6)	0.051	0.022	0.044	0.984	0.646	0.928

[a] IQD, interquartile difference.
[b] Ref, reference.

TABLE 2 Pharmacokinetics of tedizolid phosphate administered i.v. in normal humans as a single dose (17) and i.v. in infected rabbits[a]

Group and dose	C_{max}, μg/ml (n [time postdosing])	C_{min}, μg/ml (n [time postdosing])	$t_{1/2}$ (h)	AUC_{0-24}, μg · h/ml
Humans, mg q.d.				
200	2.6 ± 0.6 (9 [peak])	NA	11.0 ± 0.8	30.0 ± 10.3
400	5.1 ± 0.8 (9 [peak])	NA	11.3 ± 1.2	58.2 ± 11.4
Rabbits, mg/kg b.i.d.				
2	1.5 ± 0.7 (6 [1 h])	0.1 ± 0.1 (5 [18 h])	4.8	19.0
4	3.3 ± 1.0 (8 [1 h])	0.3 ± 0.2 (10 [18 h])	5.1	42.8
8	4.9 ± 1.2 (6 [1 h])	1.1 ± 0.5 (6 [18 h])	7.8	76.3
15	9.7 ± 1.8 (3 [1 h])	5.8 ± 2.2 (3 [9 h])	11.8	168.3

[a] C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; $t_{1/2}$, apparent terminal elimination half-life; AUC_{0-24}, area under the concentration-time curve over 24 h. NA, not available.

treated rabbits to those in vancomycin- or daptomycin-treated rabbits. Tedizolid phosphate, daptomycin, and vancomycin treatments achieved median organism titers of 2.3, 1.7, and 1.9 $\log_{10}$ CFU/g, respectively, compared to 3.4 $\log_{10}$ CFU/g for controls (Table 1).

The mean (±standard deviation) plasma concentrations of tedizolid achieved were 9.7 ± 1.8 μg/ml (n = 3) 1 h after dosing and 5.8 ± 2.2 μg/ml (n = 3) 9 h after dosing (Table 2). At 15 mg/kg b.i.d., the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) of tedizolid, the pharmacokinetic driver of efficacy (12), was 168.3 μg · h/ml, more than 5 times the AUC of 30.0 ± 10.3 μg · h/ml for the 200-mg once-daily human dose (13). Protein binding was 81.3%, independent of drug concentration over the range of 1 to 10 μg/ml, and similar to that in humans (84 to 89%) (Cubist Pharmaceuticals, data on file) (11, 14, 15). Such high drug exposures in a relatively low-inoculum infection could overestimate the activity of tedizolid *in vivo*. Accordingly, a dose-ranging study was conducted with a higher-inoculum infection to determine *in vivo* activity of tedizolid at concentrations corresponding to AUC_{0-24} values approximating those in humans.

Comparative study of tedizolid phosphate 2, 4, and 8 mg/kg i.v. b.i.d. versus vancomycin at 30 mg/kg i.v. b.i.d. at an inoculum of 10^8 CFU. Fifty-two rabbits were included in this study. Five deaths occurred during treatment: two in the 2-mg/kg b.i.d. group (one on day 1, which was not included in the data analysis, and one on day 4, which was included in the data analysis) and 3 in the 8-mg/kg b.i.d. group (one on day 3 and two on day 4, all of which were included in the data analysis). Thirteen untreated control rabbits and 9 tedizolid phosphate treated at 2 mg/kg, 11 tedizolid phosphate treated at 4 mg/kg, 10 tedizolid phosphate treated at 8 mg/kg, and 8 vancomycin treated were included in this experiment. Mean values of the AUC_{0-24} for tedizolid were 19.0, 42.8, and 76.3, respectively, for the 2-, 4-, and 8-mg/kg doses (Table 2) (16).

The burden of organisms in vegetations was significantly lower in tedizolid phosphate-treated rabbits at 4 mg/kg and 8 mg/kg, with median 0.7- and 1.1-$\log_{10}$-CFU/g decreases in titers compared to those of untreated controls, respectively (Table 3). However, tedizolid phosphate treatment at 2 mg/kg did not decrease bacterial counts compared to those in the untreated control (P = 0.857). The median vegetation titer for the tedizolid phosphate 8-mg/kg b.i.d. group was 1.1 $\log_{10}$ CFU/g higher than that for vancomycin group (median titers of 8.1 and 7.0 $\log_{10}$ CFU/g, respectively; P = 0.045). Despite the efficacy compared to the untreated control, tedizolid phosphate at 4 mg/kg was less efficacious than vancomycin (P = 0.015). Compared to tedizolid phosphate treatment at 2 mg/kg, treatments at 4 mg/kg and 8 mg/kg significantly decreased median titers by 0.8 and 1.2 $\log_{10}$ CFU/g vegetation (P < 0.001) (Table 4).

The burdens of organisms in the spleen and kidneys were significantly lower in vancomycin-treated rabbits, with median 2.8- and 2.4-$\log_{10}$-CFU/g decreases in titers, respectively, compared to the control (P < 0.001 and P = 0.002) (Table 3). Rabbits treated with tedizolid phosphate at 4 mg/kg and 8 mg/kg did not have

TABLE 3 Comparative study of tedizolid phosphate at various doses versus vancomycin

Treatment (no. of rabbits)	Median organism titer, $\log_{10}$ CFU/g (IQD)[a]			P value vs:					
				Control			Vancomycin		
	Vegetation	Spleen	Kidney	Vegetation	Spleen	Kidney	Vegetation	Spleen	Kidney
Control (13)	9.2 (0.9)	5.0 (1.2)	4.0 (1)	Ref[b]	Ref	Ref	0.002	<0.001	<0.001
Tedizolid phosphate, mg/kg b.i.d.									
2 (9)	9.3 (0.5)	5.9 (0.6)	4.8 (1.1)	0.857	0.161	0.009	0.007	<0.001	<0.001
4 (11)	8.5 (0.6)	5.4 (1.0)	4.4 (1.2)	0.004	0.722	0.598	0.015	<0.001	<0.001
8 (10)	8.1 (0.8)	5.0 (1.1)	3.6 (1.7)	<0.001	0.772	0.143	0.045	<0.001	<0.001
Vancomycin, mg/kg b.i.d.									
30 (8)	7.0 (3.7)	2.2 (1.7)	1.6 (0.8)	0.002	<0.001	<0.001	ref	ref	ref

[a] IQD, interquartile difference.
[b] Ref, reference.

TABLE 4 Statistical comparison of tedizolid phosphate at doses of 2, 4, and 8 mg/kg i.v. b.i.d.

Tedizolid phosphate dose, mg/kg i.v. b.i.d. (no. of rabbits)	Median organism titer, $\log_{10}$ CFU/g (IQD)[a]			*P* value for each treatment vs 2-mg/kg dose		
	Vegetation	Spleen	Kidney	Vegetation	Spleen	Kidney
2 (9)	9.3 (0.5)	5.9 (0.6)	4.8 (1.1)	Ref[b]	Ref	Ref
4 (11)	8.5 (0.6)	5.4 (1.0)	4.4 (1.2)	<0.001	0.036	0.095
8 (10)	8.1 (0.8)	5.0 (1.1)	3.6 (1.7)	<0.001	0.051	0.013

[a] IQD, interquartile difference.
[b] Ref, reference.

statistically significant decreases in titers for spleen or kidneys compared to the control. Tedizolid phosphate treatment at 2 mg/kg had median 0.9- and 0.8-$\log_{10}$-CFU/g increases in spleen and kidneys, respectively. Compared to tedizolid phosphate treatment at 2 mg/kg, treatments at 4 and 8 mg/kg reduced median counts of 0.5 and 0.9 $\log_{10}$ CFU/g ($P = 0.036$ and $P = 0.051$) in the spleens and 0.4 and 1.2 $\log_{10}$ CFU/g in kidneys ($P = 0.095$ and $P = 0.013$) (Table 4).

DISCUSSION

Daptomycin was the most effective antibiotic for the treatment of aortic valve endocarditis (AVE) in rabbits infected with the COL MRSA strain. Results with vancomycin and tedizolid phosphate (15 mg/kg b.i.d.) were comparable in the low-inoculum model, with modest reductions in median $\log_{10}$ colony-forming units per gram in vegetations compared to the untreated control of 2.4 and 1.5 $\log_{10}$ CFU/g, respectively. All three antibiotics had similar efficacies in eradication of organisms from spleen and kidney. The tedizolid phosphate 15-mg/kg b.i.d. dose, however, produced AUC_{0-24} values that were approximately 5 times the level achieved with once-daily dosing of 200 mg in humans (13), the dose approved for the treatment of acute bacterial skin and skin structure infections and being evaluated in nosocomial pneumonia.

To determine whether tedizolid phosphate at lower doses produces drug exposures similar to those achieved with human therapeutic doses, a second experiment with a tedizolid phosphate dose range was compared to vancomycin in a more stringent, higher-inoculum model. The 2-mg/kg b.i.d. dosing of tedizolid phosphate was not efficacious. This dose likely resulted in a subtherapeutic drug exposure, with a total drug AUC_{0-24} of approximately 60% of the human equivalent dose of 200 mg. The 4-mg/kg b.i.d. dosing resulted in an AUC_{0-24} approximately 40% higher than the 200-mg human equivalent dose and 75% of the 400-mg human equivalent dose. Given that the percentages for binding of tedizolid to human and rabbit plasma proteins are similar, free drug concentrations (and *f*AUC/MIC, the free drug AUC/MIC, the pharmacodynamic driver of efficacy [17, 18]) and exposures are likely comparable as well. However, if free drug concentrations are truly slightly higher in the rabbit, the 2-mg/kg (ineffective) dose may better reflect drug exposure for the 200-mg human dose than the 4-mg/kg dose does. Regardless, these data suggest that drug exposures in humans treated with 200 to 400 mg once daily are likely to have at most a modest bactericidal effect, corresponding to a reduction of approximately 1 $\log_{10}$ CFU in vegetations in the rabbit model, which was less effective than vancomycin. Reductions of bacterial burdens in spleen and kidney were also modest, with titers that were not statistically significantly different from that of the control and significantly higher than that for vancomycin.

The limitations of the present studies should also be considered. Only one strain, COL, was tested in this study. The treatment length was relatively brief (only 4 days), and a longer treatment may have produced more favorable results as with time the drug might accumulate in target tissues (19), increasing drug exposure. Whether there is a role for tedizolid phosphate in treatment of bacteremia from extracardiac sources also was not addressed in these experiments.

In conclusion, tedizolid phosphate had modest bactericidal activity *in vivo* and overall was less active than either vancomycin or daptomycin. The activity of tedizolid is similar to published results for linezolid in experimental endocarditis models (10, 20, 21). It seems unlikely that tedizolid, particularly at the currently recommended 200-mg dose and perhaps even at higher doses, would be effective as a sole agent or as primary therapy for treatment of endocarditis.

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