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Activities of the Oxazolidinones Linezolid and Eperezolid in Experimental Intra-Abdominal Abscess Due to *Enterococcus faecalis* or Vancomycin-Resistant *Enterococcus faecium*

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The in vivo effectiveness of oxazolidinones eperezolid (U-100592) and linezolid (U-100766) against one strain each of *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* was examined in a rat model of intra-abdominal abscess. MICs of both drugs were 2 μg/ml for each strain. At doses of 25 mg/kg of body weight twice daily intravenously or orally, linezolid produced small but statistically significant reductions in abscess bacterial density for *E. faecalis*. The reduction in viable cells observed would not likely be clinically relevant. Eperezolid was ineffective at this dose. At a dosage of 100 mg/kg/day, linezolid treatment led to an approximately 100-fold reduction in viable cells per gram of abscess. Against *E. faecium* infections, intravenous eperezolid and oral linezolid were effective, reducing densities approximately 2 $\log_{10}$ CFU/g. Both oxazolidinones demonstrated activity against enterococci in this model. However, results were modest with the dosing regimens employed.

Options for the treatment of infections due to multiply resistant enterococci are limited, and this has prompted the search for new antimicrobial agents which demonstrate activity against such strains (6). The oxazolidinones are a novel class of synthetic antimicrobials which inhibit the initiation of protein synthesis (3, 14, 23). Two compounds of this class, eperezolid (U-100592) and linezolid (U-100766) have been shown to inhibit *Enterococcus faecalis* and *Enterococcus faecium* in vitro, including strains resistant to vancomycin, at concentrations of 0.5 to 4 μg/ml (7, 13, 18, 26). These oxazolidinones are active orally and intravenously, and studies with mice have shown activity comparable to that of vancomycin against enterococci in experimental systemic and soft-tissue infections (8).

The present study was undertaken to assess the effectiveness of these compounds in a rat intra-abdominal abscess model with one strain of *E. faecalis* and one strain of vancomycin-resistant *E. faecium*.

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MATERIALS AND METHODS

Bacterial strains. *E. faecalis* 1310 is a clinical blood culture isolate, with a typical antimicrobial susceptibility profile, which we have used previously in animal models of endocarditis (10, 24). Because of the potential for spread into the laboratory environment from infected animals, instead of using a clinical strain of vancomycin-resistant *E. faecium*, we employed a penicillin-susceptible, vancomycin-resistant laboratory-derived strain designated *E. faecium* A1221. This transconjugant was selected from a cross-mating using as a donor *E. faecium* 228 (kindly provided by F. Tenover, Centers for Disease Control and Prevention), in which VanA class resistance is mediated on a conjugative plasmid (11). The recipient used was a rifampin-resistant, fusidic acid-resistant mutant derived in our laboratory from *E. faecium* SI-E20, a penicillin-susceptible strain collected in the Solomon Islands in 1968 (9).

MICs of penicillin, vancomycin, and the oxazolidinones against the two strains used in this study, obtained by agar dilution, are given in Table 1. Susceptibilities of both strains to the two oxazolidinones are typical of *E. faecalis* and (VanA) vancomycin-resistant *E. faecium* (MICs at which 50 and 90% of the isolates are inhibited = 2 μg/ml) (7).

Time-kill curves. Killing studies were performed with each strain for both oxazolidinones at concentrations 4- and 20-fold above the MICs. The experiment was carried out both in Mueller-Hinton broth and in brain heart infusion (BHI) broth (Difco Laboratories, Detroit, Mich.) for linezolid. The final inoculum consisted of stationary-phase cells suspended in broth to approximately 10^6 CFU/ml. Samples were removed at 0, 4, and 24 h from the cultures, which were incubated at 37°C without agitation, and serially diluted in saline for determinations of colony counts, which were done in duplicate.

Animal model. Enterococcal intra-abdominal abscesses were created in male Sprague-Dawley rats weighing 175 to 250 g, by using a model which has been described previously (25). For all surgical procedures rats were anaesthetized with ketamine and xylazine. Suspensions of 0.5 ml of *E. faecalis* 1310 or *E. faecium* A1221 at a density of 10^6 CFU/ml in BHI broth, along with heat-killed *Bacillus fragilis* ATCC 23745 and sterilized rat cecal contents (in ratios of 1:1:2 parts, respectively) and barium sulfate (10% [wt/vol]) were put into double-gelatin capsules which were then implanted intraperitoneally through a 1-cm midline abdominal incision.

Antimicrobial therapy. Treatment was started 4 h after implantation of the inoculum and was given either intravenously or by peroral gavage. For intravenous administration, oxazolidinones were dissolved in dimethyl sulfoxide which was diluted to 5% (vol/vol) in sterile saline. The doses used in these experiments were based on those which appeared to be active in previously published mouse protection studies (8). Antimicrobials were administered at desired intervals as 15- to 20-min infusions or by continuous infusion over 24 h via a central catheter, which was surgically implanted through the left internal jugular vein into the superior vena cava the day before the infection as previously described (24). For peroral administration, oxazolidinones were suspended in 2 ml of saline and the slurry was given by gavage every 12 h (q12h). As a positive (effective) control, ampicillin was administered by continuous intravenous infusion at a dosage of 400 mg/kg of body weight/24 h, which has previously been shown to achieve a mean steady-state serum concentration of approximately 15 μg/ml (12). Continuous-infusion therapy was administered for 4.5 days. For twice-daily regimens a total of nine doses were given over 4.5 days. Untreated control rats were included in each experiment.

Monitoring of therapy and outcome. For determination of concentrations of oxazolidinones in plasma, blood was obtained by retro-orbital puncture 0 to 5 min after completion of intermittent infusion or 45 to 60 min after gavage for peak levels and just prior to the next scheduled dose for trough levels. Samples

TABLE 1. In vitro susceptibilities of enterococci used in this study

Strain	MIC (μg/ml) of:			
	Penicillin	Vancomycin	Eperezolid	Linezolid
E. faecalis 1310	2	1	2	2
E. faecium A1221	≤0.12	128	2	2

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TABLE 2. Levels of oxazolidinones in plasma during experimental infection

Drug and dose (mg/kg)/ interval/ route[e]	Mean plasma concn (μg/ml)	
	Maximum ± SD (range)[a]	Minimum[b]
Eperezolid		
25/q12h/i.v.	22 ± 17.3 (12.3–57) [6]	0.076, 0.093
25/q12h/p.o.	0.94 ± 0.53 (0.28–1.48) [5]	0.087, 0.10
Linezolid		
25/q12h/i.v.	43.6 ± 19 (22.9–76.4) [10]	0.35 ± 0.33 (ND[c]–0.986) [7][d]
25/q12h/p.o.	3.16 ± 2.39 (0.59–5.88) [5]	ND, 0.138, 0.189
16/q4h/i.v.	57.4 [1]	14.1 [1]

[a] Numbers in bracket indicate numbers of animals sampled.
[b] Numbers of data points averaged are shown in brackets; otherwise actual values are indicated.
[c] ND, not detectable.
[d] Mean ± standard deviation and range are given.
[e] i.v., intravenous; p.o., oral.

were treated with 25 μl of 2% disodium EDTA, and plasma was separated, frozen, and sent to Pharmacia & Upjohn, where oxazolidinone concentrations were measured by high-performance liquid chromatography by Guy Padbury. Details of the assay have been published elsewhere (20). The technique has been validated to concentrations as low as 0.01 μg/ml. Coefficients of variation for intra-assay and interassay samples by this method are <10% (20).

Rats were sacrificed 12 h after the last dose of antimicrobials. The abdomen was opened under aseptic conditions, and the abscess contents were harvested, weighed, and homogenized in 2 ml of sterile saline and then serially diluted. Because of the potential for the occasional translocation of noninoculated bacteria into intra-abdominal abscess contents in the rat model of fecal peritonitis (16), suspensions were plated both on blood agar plates in duplicate for colony counts and on Enterococcosel agar plates (Becton Dickinson, Cockeysville, Md.), as a selective medium for enterococci. Plating either organism on this medium resulted in counts identical to those on blood agar plates (data not shown). Results from the selective plates were used only on those few occasions in which a question of contaminating bacteria arose. Statistical analysis was carried out by the two-tailed Mann-Whitney test. P values < 0.05 were considered statistically significant.

RESULTS

In vitro susceptibilities of test strains. Both oxazolidinones showed only bacteriostatic activity against the two strains tested at concentrations of either 4 or 20 times the MIC. Bacterial counts at 24 h were reduced by ≤ 1 $\log_{10}$ CFU/ml at the 8-μg/ml concentration. At 40 μg/ml, both agents were bacteriostatic also, with the maximum killing observed being 1.7 $\log_{10}$ CFU/ml with linezolid. Results with Mueller-Hinton broth and BHI broth were similar.

Antimicrobial levels in vivo. Levels of the oxazolidinones in plasma achieved with different treatment regimens are shown in Table 2. Considerable variability was noted in peak levels of both drugs in plasma with all regimens.

Outcome in control animals. In untreated animals inoculated with either *E. faecalis* 1310 or *E. faecium* A1221, bacterial densities within intra-abdominal abscesses reached approximately 10^8 CFU/g (Tables 3 and 4). Treatment with continuous infusion of ampicillin for 4.5 days reduced the number of viable bacteria by an average of 4.5 $\log_{10}$ CFU/g for *E. faecalis* and 6.5 $\log_{10}$ CFU/g for *E. faecium*. In both cases the effect of ampicillin was highly statistically significant.

Oxazolidinone treatment for *E. faecalis*. For eperezolid, the q12h intravenous regimen studied showed no activity against *E. faecalis*, despite mean peak levels of approximately 10 times the MIC (Table 3). Administration of the same total daily dose (50 mg/kg) by continuous 24-h infusion intravenously or by q12h oral dosing provided no advantage. Levels of linezolid in plasma were approximately twice those of eperezolid when drugs were administered at 25 mg/kg q12h intravenously and approximately three times greater when these compounds were given orally. Both routes of administration at this dosage resulted in small but statistically significant decreases in viable bacteria after 4.5 days of therapy with linezolid. Doubling the total daily dose (100 mg/kg) with more-frequent administration resulted in a 2-$\log_{10}$ CFU/g decrease in bacterial counts. No animal had sterile abscess contents.

Oxazolidinone treatment for *E. faecium*. Against this organism, intravenous and oral eperezolid, but not intravenous linezolid, reduced viable cell densities significantly. However, linezolid demonstrated activity when administered orally. Almost 2-$\log_{10}$ CFU/g reductions in residual bacteria were noted with oral linezolid and intravenous eperezolid.

DISCUSSION

The two oxazolidinones eperezolid and linezolid were previously shown to be active in vivo against *E. faecalis* and *E. faecium* in a mouse model of lethal infection in which the inoculum was injected intraperitoneally (8). For *E. faecalis*, the 50% effective dosages (ED_{50}s) of the oxazolidinones administered orally at 1 and 5 h postinfection and twice daily thereafter for 4 days were 1.3 mg/kg/day for eperezolid and 10.0 mg/kg/day for linezolid; corresponding values for *E. faecium* were 12.5 mg/kg/day for eperezolid and 24 mg/kg/day for linezolid. In the soft-tissue infection model with mice and the same strain of *E. faecalis*, ED_{50}s of eperezolid and linezolid were 20.6 and 11.0 mg/kg, respectively. This level of activity was comparable to that observed with subcutaneously administered vancomycin (ED_{50}, 16.3 mg/kg).

Our study utilized an intra-abdominal abscess model to reflect the importance of this site for enterococcal infections encountered in current practice. In a randomized, prospective

TABLE 3. Outcome of therapy for infection with *E. faecalis*

Antimicrobial	No. of animals	Dose (mg/kg)/ interval	Route of administration[b]	Mean viable bacteria in abscess ($\log_{10}$ CFU/g) ± SD [range]	P[a]
Untreated	16			8.6 ± 0.49 [8.00–9.80]	
Ampicillin	5	400/24 h[c]	i.v.c.	3.9 ± 0.54 [3.40–4.70]	0.001
Eperezolid	12	25/q12 h	i.v.	8.3 ± 0.43 [7.00–8.55]	0.17
	6	50/24 h	i.v.c.	8.9 ± 0.63 [7.74–9.47]	0.20
	12	25/q12 h	p.o.	8.3 ± 0.36 [7.75–9.06]	0.07
Linezolid	17	25/q12 h	i.v.	7.9 ± 0.77 [6.10–9.00]	0.012
	10	16.6/q4 h	i.v.	6.4 ± 0.73 [5.20–7.40]	<0.0001
	10	25/q12 h	p.o.	7.9 ± 0.21 [7.66–8.26]	<0.0001

[a] Comparison of treatment group with untreated controls.
[b] i.v., intravenous; i.v.c., continuous i.v. infusion; p.o., oral.
[c] 24 h, infusion for a 24-h period.

TABLE 4. Outcome of therapy for infection with *E. faecium*

Antimicrobial	No. of animals	Dose (mg/kg)/ interval	Route of administration[b]	Mean viable bacteria in abscess (log_{10} CFU/g) ± SD [range]	P^a
Untreated	12			8.25 ± 0.75 [7.07–9.20]	
Ampicillin	4	400/24 h[c]	i.v.c.	1.7 ± 0.54 [<1.3–2.50]	0.004
Eperezolid	20	25/q12 h	i.v.	6.5 ± 0.88 [4.47–8.27]	<0.0001
	11	25/q12 h	p.o.	7.8 ± 0.35 [7.24–8.5]	0.029
Linezolid	13	25/q12 h	i.v.	7.9 ± 0.77 [6.70–8.80]	0.46
	11	25/q12 h	p.o.	6.6 ± 0.58 [5.08–7.12]	<0.0001

[a] Comparison of treatment group with untreated controls.
[b] i.v., intravenous; i.v.c., continuous i.v. infusion; p.o., oral.
[c] 24 h, infusion for a 24-h period.

study of intra-abdominal infections, enterococci were recovered from initial cultures of percutaneous or surgical drainage in 21.5% of patients (4). The presence of enterococci on initial culture was a significant independent predictor of treatment failure in that study. Intra-abdominal infection with vancomycin-resistant *E. faecium* is a serious problem for patients who have undergone liver transplantation. In this population, Linden et al. (15) attributed vancomycin-resistant *E. faecium* bacteremia to an intra-abdominal (peritoneal space or biliary) process or deep wound infection in 78% of cases. Bacteremia with these organisms was monomicrobial in 91% of cases and was associated with mortality in 57% of cases. Among 14 patients with vancomycin-resistant *E. faecium* bacteremia who came to autopsy, the organism was recovered from visceral abscesses or the peritoneal space in 79% and was isolated as the sole pathogen in 50% (15).

The rat intra-abdominal abscess model is a rigorous test of agents for antimicrobial activity against enterococci. Agents, such as aztreonam and metronidazole, which are inactive against enterococci are not effective in the model (25). With a related model in which the inoculum consisted of mixed rat fecal flora, our previous work demonstrated the persistence of enterococci at densities of 5.6 to 7.7 log_{10} CFU/g of abscess material after therapy with various regimens which successfully reduced viable numbers of *Escherichia coli* and *B. fragilis* (19). Thus, only regimens with activity against the enterococci specifically show effectiveness against the organism in these models.

In the present study, peroral administration of equal doses of eperezolid and linezolid resulted in higher peak levels of the latter drug in plasma, which may explain its activity against both infecting strains when administered by this route and the lesser effect of eperezolid. Although peak levels of linezolid were higher than those of eperezolid when equivalent doses were administered intravenously, which correlated with the greater effectiveness of the former against *E. faecalis*, it is not clear why the opposite effect against *E. faecium* was seen. The levels achieved in this model following administration of eperezolid intravenously closely reproduced peak and trough levels seen in human volunteers who received 1 g of this agent q6h (26.23 and 0.95 μg/ml, respectively) (21).

Although statistically significant antibacterial effects were observed with both oxazolidinones when they were administered at the dosage of 25 mg/kg twice daily, the actual reductions in bacterial densities of *E. faecalis* in animals treated with linezolid were of a magnitude that would be of unclear clinical significance. Doubling the total daily dose of linezolid, with more-frequent dosing, resulted in an approximately 2-log_{10} CFU/g reduction in bacterial density. This observation suggests that the other doses or regimens used in this study may not have been optimal for treatment of enterococcal infection in rats. Furthermore, no oxazolidinone regimen yielded results comparable to those seen with ampicillin in this model. In part, this may be due to the bacteriostatic activity of the oxazolidinone against enterococci (7). To date, there is no evidence that the combination of oxazolidinones with other agents which might be active against enterococci would further enhance their antibacterial activities, and some combinations (eperezolid plus clinafloxacin) may even be antagonistic (2, 17).

This study was not designed to assess the pharmacodynamic behavior of the oxazolidinones or to examine in detail their pharmacokinetics in rats. With an estimated elimination half-life of approximately 1 h in Sprague-Dawley rats following intravenous infusion of linezolid at 10 mg/kg (5), we could estimate the percentage of time above MIC to have been approximately 38% of the dosing interval, based on peak serum levels achieved in our animals after the 25-mg/kg dose. This is near the lower end of the range of values (33 to 59%) associated with a bacteriostatic effect in the treatment of staphylococcal infections in a mouse model (1). This may explain the modest effects observed in our study.

However, there are two lines of reasoning to suggest that the percentage of time above MIC in plasma may not be a particularly accurate predictor of response in this model. First, in our infected rats receiving multiple doses of linezolid at 25 mg/kg q12h, it would appear from examination of an admittedly small number of data points that the terminal half-life may have been closer to 1.75 h. In that case, the percentage of time above MIC would have been closer to 60% for both linezolid and eperezolid. Second, although measurements of plasma concentrations were not available for rats treated with a continuous infusion of eperezolid, based on concentrations achieved with q12h dosing we estimated plasma levels of approximately twice the MIC for the entire dosing interval. It would thus appear that plasma concentrations substantially in excess of the MIC for a significant percentage of the dosing interval are required for demonstration of significant reduction in bacterial densities by these bacteriostatic agents in our model.

We have confirmed previous observations documenting the in vivo activity of the oxazolidinones eperezolid and linezolid in experimental enterococcal infection. Nevertheless, effects were modest and therefore of uncertain clinical relevance. Further studies using optimized dosing based on comparative pharmacokinetics in humans and experimental animals and on the results of safety and tolerability profiles from clinical trials with the oxazolidinones may be appropriate.

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