ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2004, p. 1708–1712 Vol. 48, No. 5
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.5.1708–1712.2004

In Vivo Efficacy and Pharmacokinetics of AC98-6446, a Novel Cyclic Glycopeptide, in Experimental Infection Models

William J. Weiss,[1]* Timothy Murphy,[1] Eileen Lenoy,[1] and Mairead Young[2]

Infectious Disease Section,[1] Discovery Analytical Chemistry,[2] Wyeth Research, Pearl River, New York 10965

Received 8 October 2003/Returned for modification 19 December 2003/Accepted 29 January 2004

AC98-6446 is a novel semisynthetic derivative of a natural product related to the mannopeptimycins produced by *Streptomyces hygroscopicus*. Naturally occurring esterified mannopeptimycins exhibited excellent in vitro activity but only moderate in vivo efficacy against staphylococcal infection. The in vivo efficacy and pharmacokinetics of AC98-6446 were investigated in murine acute lethal, bacterial thigh and rat endocarditis infections. Pharmacokinetics were performed in mice, rats, monkeys, and dogs. Acute lethal infections were performed with several gram-positive isolates: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant staphylococci), vancomycin-resistant *Enterococcus faecalis*, and penicillin-susceptible and -resistant *Streptococcus pneumoniae*. The 50% effective dose for all isolates tested ranged from 0.05 to 0.39 mg/kg of body weight after intravenous (i.v.) administration. Vancomycin was more than fivefold less efficacious against all of these same infections. Results of the thigh infection with *S. aureus* showed a static dose for AC98-6446 of 0.4 mg/kg by i.v. administration. Reduction of counts in the thigh of >2 $\log_{10}$ CFU were achieved with doses of 1 mg/kg. i.v. administration of 3 mg/kg twice a day for 3 days resulted in a >3 $\log_{10}$ reduction in bacterial counts of vancomycin-susceptible and -resistant *E. faecalis* in a rat endocarditis model. Pharmacokinetics of AC98-6446 showed an increase in exposure (area under the concentration-time curve) from mouse to dog species. The i.v. half-life ($t_{1/2}$) increased threefold between rodents and the higher species dosed. Efficacy of AC98-6446 has been demonstrated in several models of infection with resistant gram-positive pathogens. This glycopeptide exhibited bactericidal activity in these models, resulting in efficacy at low doses with reduction in bacterial load.

Staphylococci and enterococci are the cause of many hospital and community-acquired infections. The severity of these infections can range from skin and skin and skin structure infections to septic arthritis, osteomyelitis, and prosthetic valve endocarditis (9, 12).

The methicillin-resistant staphylococci (MRSA) are prevalent in most major medical centers, compromising a large percentage of staphylococcal infections encountered. The incidence of these isolated pathogens has continued to increase. Their prevalence varies by geographic regions, but they remain a clinical problem due to multidrug resistance (22). Decreased susceptibility to erythromycin, gentamicin, tetracycline, rifampin, and the fluoroquinolones severely limits the therapeutic options for treatment of patients with severe MRSA infections (6). Glycopeptide-intermediate *Staphylococcus aureus* strains were first identified in the late 1990s, with the first reported vancomycin-resistant strain recently isolated from a patient in a Michigan medical center (14). Staphylococcal strains with reduced susceptibility to vancomycin have now been identified in several countries (3, 13).

Glycopeptide resistance in enterococci is recognized as a clinical problem of increasing importance (7). In particular, vancomycin-resistant *Enterococcus* (VRE) represents an important nosocomial pathogen capable of spread from colonized infected patients to uncolonized ones (30). Since it was first isolated in Europe in 1986, VRE has reached upwards of 26% in isolates tested from intensive care units in the United States (2). The intrinsic resistance of the enterococci precludes the use of conventional antibiotic therapy (1, 21).

AC98-6446 (Fig. 1), the ketal derivative of a core-modified mannopeptimycin, is a semisynthetic glycopeptide derived from *Streptomyces hygroscopicus* (8, 28). Esterified mannopeptimycins produced from this organism have demonstrated excellent in vitro activity. MICs of 0.03 to 0.06 μg/ml have been exhibited by AC98-6446 against methicillin-susceptible and -resistant staphylococci. In vitro activity against vancomycin-susceptible and -resistant enterococci has been demonstrated at concentrations of 0.12 to 0.25 μg/ml and ≤0.008 μg/ml for *Streptococcus pneumoniae* (P. Petersen, P. Labthavikul, T. Wang, R. Dushin, and P. Bradford, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-353, 2002). Additionally, AC98-6446 has been shown to be bactericidal, exhibits a long (2 to 4 h) gram-positive postantibiotic effect (P. Petersen, H. Hartman. T. Wang, R. Dushin, and P. Bradford, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-354, 2002), and exhibits limited inoculum effect and activity against adherent cells in a biofilm (P. Labthavikul, P. Petersen, T. Wang, R. Dushin, and P. Bradford, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-355, 2002). These properties make it a potential candidate for treatment of serious infection caused by resistant staphylococci and enterococci.

The present study was undertaken to evaluate the in vivo efficacy of AC98-6446 in several experimental infection models with these organisms as well as to assess the pharmacokinetics of the compound in several species.

(Data from this study were presented in part at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., 27 to 30 September, 2002 [T. Murphy, E. Lenoy, M. Young, and W. Weiss, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-356, 2002].)

* Corresponding author. Present address: Cumbre Inc., 1502 Viceroy Dr., Dallas, TX 75235-2304. Phone: (214) 631-4700. Fax: (214) 631-4710. E-mail: williamweiss@cumbre.biz.

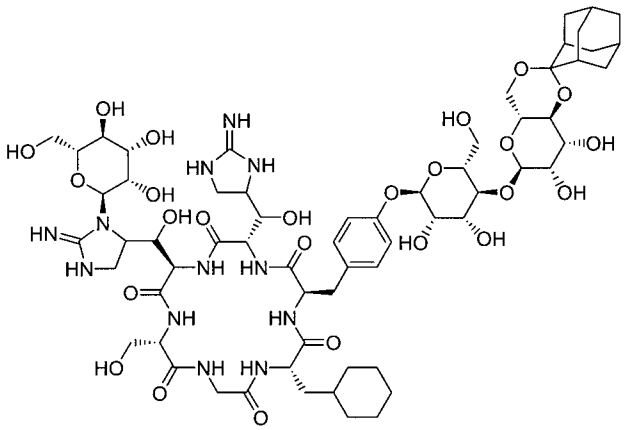

FIG. 1. Chemical structure of AC98-6446.

MATERIALS AND METHODS

Organisms. All organisms used in this study were taken from the Wyeth Research culture collection and represent recent clinical isolates collected from various medical centers around the United States. Standard laboratory strains of *S. pneumoniae* ATCC 1894 and ATCC 6301 were obtained from the American Type Culture Collection (Rockville, Md.).

Compounds. AC98-6446 was prepared by Wyeth Research (Pearl River, N.Y.), and vancomycin was obtained from Sigma Chemical Corp. (St. Louis, Mo.). AC98-6446 was prepared in 5% dextrose water, and vancomycin was prepared in sterile saline for all the models performed.

Acute lethal infection model. Female mice, strain CD-1 (Charles River Laboratories, Kingston, N.Y.), 20 ± 2 g of body weight each, were challenged by intraperitoneal injection of bacterial cells from 5-h broth cultures suspended in either trypticase soy broth or 5% hog gastric mucin. Five animals were infected at each of five i.v.-administered dose levels, covering a twofold dilution series for AC98-6446 and vancomycin for each organism. The bacterial inoculum level for infection was sufficient to result in death of untreated controls within 24 to 48 h. The 7-day survival ratios from three separate tests were pooled for estimation of the 50% effective dose (ED_{50}) by a computerized program for probit analysis (5). All procedures were carried out by using protocols approved by the Wyeth Research Animal Care and Use Committee.

Murine thigh infection model. Female CD-1 mice (Charles River Laboratories) weighing 18 to 22 g were rendered neutropenic by intraperitoneal injection of Cytoxan (cyclophosphamide) on days −4 (150 mg/kg of body weight) and −1 (100 mg/kg) before infection. On the day of infection, random colonies of *Staphylococcus aureus* Smith were selected off a trypticase soy agar plate that was incubated for 24 h at 37°C by using the Prompt inoculation system (BBL Microbiology Systems, Sparks, Md.). This was then diluted in trypticase soy broth to yield a final bacterial concentration of 10^7 CFU/ml. The thigh infection was induced by intramuscular injection of 0.1 ml of the inoculum into the left thigh of each mouse 1.5 h prior to initiation of treatment. AC98-6446 was administered by intravenous injection of 0.2 ml in twofold dilutions ranging from 0.06 to 16 mg/kg with three mice per dose level. Mice were euthanized 24 h after dose administration and thighs were removed, homogenized, and plated for determination of viable bacteria. The limit of detection of bacterial counts was 10^2 CFU/thigh. Counts were analyzed by using a sigmoid E_{max} model (WinNonlin Pro, version 3.0; Pharsight Corporation, Mountain View, Calif.).

Rat endocarditis. Endocarditis was produced in male Wistar rats (250 g; Charles River Laboratories) by insertion of a sealed polyethylene cannula (PE10) through the right carotid artery into the left ventricle; the cannula was sutured in place as a point of adherence for bacterial infection (5, 6, 15). At 48 h after implantation of the cannula, a 5-h bacterial culture was diluted to 10^5 to 10^6 CFU/ml in sterile saline, and 1 ml was injected i.v. (5). Isogenic strains of *Enterococcus faecalis* were used: GC 6181, a vancomycin-susceptible isolate, and GC 6191, its isogenic vancomycin-resistant (VanA) derivative. Inoculum infection concentration was verified by plate counts. Antibacterial treatment was initiated 24 h after bacterial challenge. Treatments were delivered by intravenous administration every 12 h for 3 days. The dose ranges tested were from 1 to 10 mg/kg/day. Untreated control rats received injections of phosphate-buffered saline. Both treated and control rats were euthanized by CO_2 inhalation 24 h after the last treatment. Hearts were aseptically removed, weighed, homogenized, and serially diluted in saline for determination of viable bacteria (the limit of detection was 10^2 CFU/heart), expressed as $\log_{10}$ CFU per heart.

Pharmacokinetics. The pharmacokinetics of AC98-6446 were investigated in the mouse, rat, dog, and monkey. Female CD-1 mice (Charles River Laboratories) weighing 18 to 22 g were administered a single dose of AC98-6446 i.v. at 20 mg/kg. Blood samples were taken at selected time points by cardiac puncture, and the blood from three mice was pooled for serum collection at each time point. Male Wistar rats (250 g; Charles River Laboratories) received 20 mg of AC98-6446/kg by i.v. injection. Three rats were used for each dose tested. Blood samples were obtained via a surgically implanted jugular cannula at selected time points. Female beagle dogs (9 to 12 kg) and female cynomolgus monkeys (4 to 6 kg) were administered AC98-6446 by i.v. injection of 20 mg/kg. Three animals were used for each species at each dose. Blood samples were collected from the femoral artery for analysis at selected time points.

Sample analysis. Analysis of the pharmacokinetic samples was performed by LC-MS (HP1100) via direct injection of the plasma sample (10 μl). A gradient of 10 to 60% (0.02% trifluoracetic acid) acetonitrile over 15 min was used in a Prodigy ODS3 (dimensions, 4.6 by 150 mm, 5-μm column; flow rate, 1 ml/min). Detection was performed by using an MSD detector (single ion monitoring at 717.5; fragmentor, 100; gain, 1) (Agilent Technologies, Palo Alto, Calif.). Limit of detection of AC98-6446 was 50 ng/ml. Pharmacokinetic parameters were determined by using the WinNonlin program (WinNonlin Pro, version 3.0; Pharsight Corporation).

RESULTS

Acute lethal infection model. The efficacy of AC98-6446 and vancomycin were determined against infections with methicillin-susceptible and -resistant *S. aureus*, vancomycin-resistant *E. faecalis,* and penicillin-susceptible and -resistant *S. pneumoniae* isolates (Table 1). AC98-6446 demonstrated efficacy against both methicillin-susceptible and -resistant *S. aureus* infections regardless of methicillin susceptibility. ED_{50}s of 0.08 and 0.27

TABLE 1. In vivo efficacy of i.v.-administered AC98-6446 and vancomycin against gram-positive pathogens in a murine acute lethal infection model

Compound[c]	ED_{50} in mg/kg (95% confidence limits[a])				
	S. aureus (MSSA)	*S. aureus* (MRSA)	*E. faecalis* (VRE)	*S. pneumoniae* (Pen^{r}[b])	*S. pneumoniae* (Pen^{s}[b])
AC98-6446	0.08 (0.07–0.11)	0.27 (0.21–0.34)	0.39 (0.32–0.48)	0.05 (0.04–0.07)	0.07 (0.05–0.09)
Vancomycin	0.69 (0.51–0.97)	2.89 (1.87–7.0)	20 (10.8–44.3)	0.4 (0.31–0.52)	1.55 (1.27–1.89)
LD_{50}[d]	1.3×10^5	1.1×10^6	1.6×10^6	1.0×10^1	1.8×10^1

[a] Seven-day survival ratio from three separate tests, pooled for estimation of ED_{50} and 95% upper and lower confidence limits by a computerized program for joint probit analysis.

[b] Pen^{r}, penicillin-resistant ATCC1894; Pen^{s}, penicillin-susceptible ATCC6301.

[c] AC98-6446 MIC (micrograms per milliliter) for *S. aureus* (MSSA), 0.03; *S. aureus* (MRSA), 0.015; *E. faecalis*, 0.06; *S. pneumoniae* (Pen^{r}), <0.008; *S. pneumoniae* (Pen^{s}), <0.008. Vancomycin MIC for *S. aureus* (MSSA), 1; *S. aureus* (MRSA), 0.5; *E. faecalis*, >8; *S. pneumoniae* (Pen^{r}), <0.5; *S. pneumoniae* (Pen^{s}), 0.25.

[d] LD_{50}, 50% lethal dose.

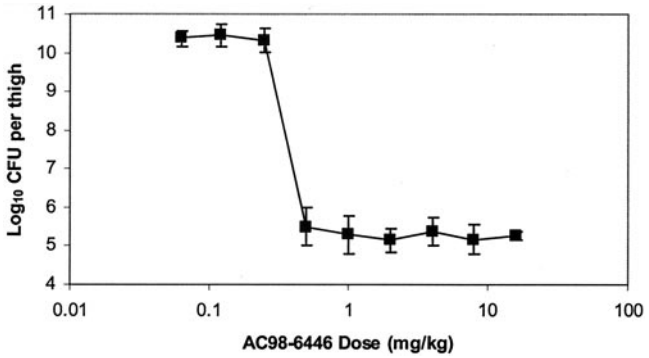

FIG. 2. Bacterial counts in thighs of mice infected with *S. aureus* Smith. AC98-6446 was administered i.v. as a single dose at 1.5 h postinfection. Bacterial titers were determined 24 h after infection. Mean values ± standard deviation are represented for three mice at each dose level.

TABLE 2. Efficacy of AC98-6446 against experimental endocarditis caused by isogenic strains of *E. faecalis*

Organism	Treatment	*n*	Dose (mg/kg/day)	Bacterial titer (log_{10} CFU/heart)		Reduction from control (log_{10} CFU)
				Mean	SD	
GC 6181	None	22	0	9.52	0.90	
	AC98-6446	8	1.0	8.37	0.79	−1.16[a]
	AC98-6446	8	2.0	7.56	1.07	−1.96[a]
	AC98-6446	14	6.0	5.64	0.82	−3.88[a]
	AC98-6446	9	10.0	5.69	1.22	−3.84[a]
GC 6191	None	22	0	9.96	1.28	
	AC98-6446	12	1.0	7.43	1.12	−2.53[a]
	AC98-6446	9	2.0	7.68	1.12	−2.29[a]
	AC98-6446	8	6.0	5.38	0.92	−4.58[a]
	AC98-6446	9	10.0	4.04	0.78	−5.92[a]

[a] Statistically significant difference ($P < 0.001$) as determined by *t* test.

mg/kg were achieved against the methicillin-susceptible *S. aureus* (MSSA) and MRSA strains, respectively. Vancomycin was approximately 10 times less potent than AC98-6446, with ED_{50}s of 0.69 and 2.89 mg/kg for the MSSA and MRSA infections, respectively. AC98-6446 maintained its excellent efficacy against a VRE infection (ED_{50}, 0.39 mg/kg). Vancomycin, as expected, required a much higher dose to protect mice from infection with the VRE organism. Efficacy of AC98-6446 against the penicillin-susceptible and -resistant *S. pneumoniae* isolates was comparable, with ED_{50}s of 0.05 to 0.07 mg/kg, respectively. AC98-6446 was 8 to 22 times more effective than vancomycin against these infections. The efficacy of vancomycin decreased between the susceptible and resistant *S. pneumoniae* infection, demonstrated by an increase in ED_{50} from 0.4 to 1.55 mg/kg. Overall, AC98-6446 demonstrated excellent in vivo efficacy in this model against all the isolates tested. This data correlates well with previously observed in vitro activity (P. Petersen, P. Labthavikul, T. Wang, R. Dushin, and P. Bradford, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-353, 2002).

Murine thigh infection model. Figure 2 shows the effect of i.v. administration of AC98-6446 to neutropenic CD-1 mice infected intramuscularly with *S. aureus* Smith. AC98-6446 was administered 1.5 h after infection as a single dose over a range from 0.06 to 16 mg/kg. The bacterial density taken from control animals prior to initiation of dosing was determined to be 7.2 ± 0.35 log_{10} CFU/thigh, which increased to 11.2 ± 0.78 log_{10} CFU/thigh after 24 h in the untreated controls. The maximal effect represented by a 2 log_{10} reduction in counts was observed for doses exceeding 0.5 mg/kg. The dose that resulted in no change of bacterial growth from the initial titer (static dose) was determined to be 0.39 mg/kg. The EC_{50}, or dose resulting in 50% of maximal bacterial killing, was 0.37 mg/kg, with an E_{max} value of 5.2 CFU/thigh. AC98-6446 exhibited an extreme difference in bactericidal activity between the 0.25 and 0.5 mg/kg doses. The twofold dose level change resulted in a 4.5 log_{10} difference in bacterial thigh density. The steep dose response between these two doses represents the difference from no effect to maximal effect observed with all doses administered.

Rat endocarditis. Bacterial vegetation densities were determined in untreated controls at the end of therapy for *E. faecalis* GC 6181 and at both the initiation and end of therapy for GC 6191. Results are shown in Table 2. The mean bacterial density for untreated control animals (mean log_{10} numbers of CFU per heart ± the standard deviation) at 4 days after bacterial challenge for GC 6181 was 9.52 ± 0.9. Mean bacterial densities for GC 6191 untreated controls at initiation of therapy and after 4 days were 7.39 ± 0.7 and 9.96 ± 1.2, respectively. Both *E. faecalis* cardiac infections were treated i.v. with AC98-6446 administered twice a day for total daily doses of 1, 2, 6, and 10 mg/kg. Against *E. faecalis* GC 6181, a vancomycin-susceptible strain, AC98-6446 demonstrated a dose response reduction in viable bacterial counts compared to counts observed in infected control animals. A dose of 2 mg/kg/day resulted in vegetative counts that were 1.96 log_{10} lower than those of untreated animals at the end of therapy. Increasing the dose to 6 and 10 mg/kg/day resulted in bacterial reductions of 3.88 and 3.84 log_{10} CFU, respectively. Total doses of 1, 2, 6, and 10 mg/kg/day of AC98-6446 administered to animals infected with *E. faecalis* GC 6191 (vancomycin-resistant) resulted in bacterial count reductions of 2.53, 2.29, 4.58, and 5.92 log_{10} CFU from untreated control titers at the end of therapy, respectively. Compared to the bacterial counts at the initiation of therapy, doses of 6 and 10 mg/kg/day resulted in titer reductions of 2.01 log_{10} and 3.35 log_{10}, respectively. AC98-6446 therefore demonstrated a bactericidal effect (>3 log_{10}) for the vancomycin-resistant *E. faecalis* infection when administered at 10 mg/kg/day.

Pharmacokinetics. The pharmacokinetics of i.v.-administered AC98-6446 in four species are shown in Table 3. The maximum observed concentration of AC98-6446 after 20-mg/kg i.v. administration to mice, rats, monkeys, and dogs was 31.6, 231, 188, and 201 μg/ml, respectively. The compound demonstrates increased exposure as measured by the area under the concentration curve with higher species. The area under the concentration curve increases from 164 μg · h/ml in mice to 241 μg · h/ml in rats, 860 μg · h/ml in monkeys, and 1,247 μg · h/ml in dogs. The observed increased exposure corresponds to a decreased clearance of the compound from the plasma in the higher species. Clearance values (in millili-

TABLE 3. Pharmacokinetic parameters for AC98-6446 following i.v. administration of a single 20-mg/kg dose to mice, rats, monkeys, and dogs

Animal	C_{max} (μg/ml)	AUC (μg/h/ml)	$t_{1/2}$ (h)	CL (ml/h/kg)	V_{ss} (liters/kg)
Mouse	316	164	3.3	121	1.8
Rat	231	241	1.5	83	0.21
Monkey	188	860	11.5	23	0.2
Dog	201	1,247	11	16	0.3

[a] C_{max}, maximal concentration observed; AUC, area under the concentration curve; $t_{1/2}$, plasma half-life; CL, clearance; V_{ss}, volume of distribution at steady state.

ters per hour per kilogram) decrease from 121 and 83 in the mouse and rat to 23 and 16 in the monkey and dog. The plasma $t_{1/2}$ also reflects this with values of 3.3, 1.5, 11.5, and 11 h observed for the mouse, rat, monkey, and dog, respectively.

DISCUSSION

The increase in the number of gram-positive bacteria with multidrug resistance occurring in the last several years has resulted in infections that are difficult to treat. This is of particular concern regarding staphylococci and enterococci. The incidence of MRSA has risen to be the cause of up to 21% of skin infections and 59% of nosocomial pneumonia in certain areas (20). Infections with MRSA have become a concern in long-term care facilities from patients colonized with MRSA in hospitals prior to transfer to the facility (15). Until recently, vancomycin has been the drug of choice for these infections (24). However, the emergence of *S. aureus* with reduced susceptibility to vancomycin has been reported from the United States, France, Spain, United Kingdom, Japan, Korea, and China (29). These isolates, with vancomycin MICs ranging from 4 to 8 μg/ml, have been referred to as VISA, for vancomycin-intermediate *S. aureus* (13). Many of these isolates exhibiting reduced susceptibility to the glycopeptides have been associated with therapeutic failures with vancomycin (29). Resistance has been reported to be associated with increased cell wall synthesis and a thickened or aggregated cell wall (23). Infections with these isolates represents a therapeutic challenge.

The enterococci have emerged as an increasingly important pathogen because of acquired resistance to the glycopeptides (VRE) and other agents. Glycopeptide resistance rates vary from extremely low for *E. faecalis* in the Asia Pacific and Latin America to over 50% for *E. faecium* in North America (17). VRE colonization appears to be more frequent than actual infection (11) and predominates in the intensive care unit, with nosocomial transmission a particular concern (19, 21). Resistance rates for vancomycin and some of the newer agents underscore the need for alternative therapy (10, 18, 27).

AC98-6446 is a semisynthetic derivative belonging to the mannopeptimycin family of glycopeptide antibiotics that selectively targets bacterial cell wall synthesis (25). It has been shown to be a potent bactericidal inhibitor of resistant gram-positive bacteria, including methicillin-resistant and glycopeptide-intermediate *S. aureus* as well as vancomycin-resistant *E. faecalis* and *E. faecium* (Petersen et al., 42nd ICAAC). The in vitro activity observed in these studies was also exhibited by in vivo efficacy.

Our results indicate that AC98-6446 was more effective than vancomycin against infections with MSSA and MRSA, vancomycin-resistant *E. faecalis*, and penicillin-susceptible and -resistant *S. pneumoniae*. Efficacy of AC98-6446 was not dependent on the resistance phenotype of the organism. We observed equivalent efficacy regardless of methicillin resistance in *S. aureus* or penicillin resistance in *S. pneumoniae*. Of particular note is that AC98-6446 was over 10 and 50 times more efficacious than vancomycin against infections with the MRSA and VRE strains, respectively.

As previously reported, AC98-6446 exhibited bactericidal activity against staphylococci, streptococci, and enterococci as well as a long postantibiotic effect (Petersen et al., 42nd ICAAC). The results of the thigh infection model from this study show a sharp decline in bacterial counts in infected thighs within a twofold dose range. Increasing the dose administered from 0.25 to 0.5 mg/kg resulted in the difference between a 3 $\log_{10}$ increase and a 1.5 $\log_{10}$ decrease from the initial infection level. Increasing doses up to 16 mg/kg did not affect the observed bactericidal activity of the compound. Further pharmacodynamic studies are required to assess the implications of this and the parameters required for efficacy of the compound.

Infective endocarditis due to complications from intravenous drug use, prosthetic valves, and nosocomial bacteremia results in extended hospital stays and high mortality rates (26). This is especially true when infection is due to VRE or MRSA (4). AC98-6446 was clearly effective in preventing growth of both vancomycin-susceptible and vancomycin-resistant *E. faecalis* isolates in an infective endocarditis model. It exhibited greater efficacy at a lower dose than was previously reported for vancomycin against these same strains (1.5 and 0.14 $\log_{10}$ reduction against GC 6181 and GC 6191, respectively, at a dose of 40 mg/kg/day) (16). In addition, bactericidal activity (>3 $\log_{10}$ reduction in viable counts) was observed against the VRE strain from counts at the initiation of therapy. These results underscore the excellent activity of AC98-6446 against VRE in addition to its ability to treat this difficult deep-seated infection.

The infection models described in this study involved the use of rodent species (mouse and rat) only. Pharmacokinetic exposure of AC98-6446 was moderate in the mouse and rat, with $t_{1/2}$ of 3.3 and 1.5 h and plasma clearance of 121 and 83 ml/h/kg. Higher species (monkey and dog) exhibited longer plasma exposure and slower clearance values. Efficacy, if related to overall exposure, could therefore require a lower administered dose in higher species.

Overall, AC98-6446, representative of a novel class of glycopeptide antibiotics, exhibits excellent in vitro activity against resistant gram-positive pathogens, which was also demonstrated in vivo in three different animal models of infection. Efficacy against infections involving MRSA and vancomycin-resistant *E. faecalis* and an acceptable pharmacokinetic profile coupled with a unique mechanism of action (A. Ruzin, G. Singh, A. Severin, Y. Yang, R. Dushin, A. Sutherland, A. Minnick, M. Greenstein, M. May, D. Shlaes, and P. Bradford, unpublished results) make this compound an excellent candidate for further study.

ACKNOWLEDGMENTS

We greatly appreciate and recognize the contributions of Pete Petersen, Russell Dushin, Patricia Bradford, Raymond Testa, Steve Projan, John O'Connell, David Shlaes, and Tarek Mansour.

REFERENCES

1. **Calderon, E., J. Arredo-Garcia, F. Aguilar, and P. Garcia-Roca.** 2003. In vitro antimicrobial susceptibility in clinical isolates of Enterococcus species. Salud Publica de Mexico **45:**96–101.
2. **Chavers, L., S. Moser, W. Benjamin, S. Banks, J. Steinhauer, A. Smith, C. Johnson, E. Funkhouser, L. Chavers, A. Stamm, and K. Waites.** 2003. Vancomycin-resistant Enterococci: 15 years and counting. J. Hosp. Infect. **53:** 159–171.
3. **Denis, O., C. Nonhoff, B. Byl, C. Knoop, S. Bobin, and M. Struelens.** 2002. Emergence of vancomycin-intermediate *Staphylococcus aureus* in a Belgian hospital. J. Antimicrob. Chemother. **50:**383–391.
4. **Eliopoulos, G.** 1992. Enterococcal endocarditis, p. 209–223. *In* D. Kaye (ed.), Infective endocarditis, 2nd ed. Raven Press Ltd., New York, N.Y.
5. **Finney, D.** 1971. Probit analysis, 3rd ed. Cambridge University Press, London, United Kingdom.
6. **Fluit, A., C. Wielders, J. Verhoef, and F. Schmitz.** 2001. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY study. J. Clin. Microbiol. **39:**3727–3732.
7. **Grohskopf, L., R. Sinkowitz, D. Garrett, A. Sohn, G. Levine, J. Siegel, B. Stover, and W. Jarvis.** 2002. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J. Pediatr. **140:** 432–438.
8. **He, H., T. Williamson, B. Shen, E. Graziani, H. Yang, S. Sakya, P. Petersen, and G. Carter.** 2002. Mannopeptimycins, novel antibacterial glycopeptides from *Streptomyces hygroscopicus*, LL-AC98. J. Am. Chem. Soc. **124:**9729–9736.
9. **Joels, C., B. Matthews, L. Sigmon, R. Hansan, C. Lohr, K. Kercher, J. Norton, R. Sing, and B. Heniford.** 2003. Clinical characteristics and outcomes of surgical patients with vancomycin-resistant enterococcal infections. Am. Surg. **69:**514–519.
10. **Johnson, A., M. Warner, G. Hallas, and D. Livermore.** 2000. Susceptibility to quinupristin/dalfopristin and other antibiotics of vancomycin-resistant enterococci from the UK, 1997 to mid-1999. J. Antimicrob. Chemother. **46:** 125–128.
11. **Lai, K., S. Fontecchio, A. Kelly, S. Baker, and Z. Melvin.** 2003. The changing epidemiology of vancomycin-resistant enterococci. Infect. Control Hosp. Epidemiol. **24:**264–268.
12. **Lepelletier, D., and H. Richet.** 2001. Surveillance and control of methicillin-resistant *Staphylococcus aureus* infections in French hospitals. Infect. Control Hosp. Epidemiol. **22:**677–682.
13. **Linares, J.** 2001. The VISA/GISA problem: therapeutic implications. Clin. Microbiol. Infect. **7**(Suppl. 4)**:**8–15.
14. **Livermore, D.** 2000. Antibiotic resistance in staphylococci. Int. J. Antimicrob. Agents **16**(Suppl. 1)**:**S3–S10.
15. **Mendelson, G., Y. Yearmack, E. Granot, J. Ben-Israel, R. Colodner, and R. Raz.** 2003. *Staphylococcus aureus* carrier state among elderly residents of a long term care facility. J. Med. Direct. Assoc. **4:**125–127.
16. **Murphy, T., J. Deitz, P. Petersen, S. Mikels, and W. Weiss.** 2000. Therapeutic efficacy of GAR-936, a novel glycylcycline, in a rat model of experimental endocarditis. Antimicrob. Agents Chemother. **44:**3022–3027.
17. **Mutnick, A., D. Biedenbach, and R. Jones.** 2003. Geographic variations and trends in antimicrobial resistance among Enterococcus faecalis and Enterococcus faecium in the SENTRY Program. Diagn. Micrbiol. Infect. Dis. **46:**63–68.
18. **Nilius, A.** 2003. Have the oxazolidinones lived up to their billing? Future perspectives for this antibacterial class. Curr. Opin. Investig. Drugs **4:**149–155.
19. **Pacio, G., P. Visintainer, G. Maguire, G. Wormser, J. Raffalli, and M. Montecalvo.** 2003. Natural history of colonization with vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and resistant grampositve bacilli among long term care facility residents. Infect. Control Hosp. Epidemiol. **24**:246–250.
20. **Pechere, J.** 1999. Current and future management of infections due to methicillin-resistant staphylococci infections: the role of quinupristin/dalfopristin. J. Antimicrob. Chemother. **44**(Suppl. A):11–18.
21. **Rahim, S., S. Pillai, H. Gold, L. Venkataraman, K. Inglima, and R. Press.** 2003. Linezolid-resistant, vancomycin-resistant Enterococcus faecium infection in patients without prior exposure to linezolid. Clin. Infect. Dis. **36:**146–148.
22. **Rennie, R., R. Jones, and A. Mutnick.** 2003. Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). Diagn. Microbiol. Infect. Dis. **45:**287–293.
23. **Rybak, M., and R. Akins.** 2001. Emergence of methicillin-resistant Staphylococcus aureus with intermediate glycopeptide resistance: clinical significance and treatment options. Drugs **61:**1–7.
24. **Sieradzki, K., T. Leski, J. Dick, L. Borio, and A. Tomasz.** 2003. Evolution of a vancomycin-intermediate *Staphylococcus aureus* strain in vivo: multiple changes in the antibiotic resistance phenotypes of a single lineage of methicillin-resistant *S. aureus* under the impact of antibiotics administered for chemotherapy. J. Clin. Microbiol. **41:**1687–1693.
25. **Singh, M., P. Petersen, W. Weiss, J. Janso, S. Luckman, E. Lenoy, P. Bradford, R. Testa, and M. Greenstein.** 2003. Mannopeptimycins, new cyclic glycopeptide antibiotics produced by *Streptomyces hygoscopicus* LL-AC98: antibacterial and mechanistic activities. Antimicrob. Agents Chemother. **47:** 62–69.
26. **Sobel, J.** 1992. Nosocomial infective endocarditis, p. 316. *In* D. Kaye (ed.), Infective endocarditis, 2nd ed. Raven Press Ltd., New York, N.Y.
27. **Strahilevitz, J., and E. Rubenstein.** 2002. Novel agents for resistant grampositive infections–a review. Inter. J. Infect. Dis. **6**(Suppl. 1)**:**S38–S46.
28. **Sum, P., D. How, N. Torres, P. Petersen, E. Lenoy, W. Weiss, and T. Mansour.** 2003. Novel ether derivatives of mannopeptimycin glycopeptide antibiotic. Bioorg. Med. Chem. Lett. **13:**1151–1155.
29. **Tenover, F.** 1999. Implications of vancomycin-resistant Staphylococcus aureus. J. Hosp. Infect. **43**(Suppl.)**:**S3–S7.
30. **Zhang, Y., S. Geng, F. Lai, and N. Wang.** 2002. Survey of drug resistance to ciprofloxacin in common pathogenic bacteria. Di Yi Jun Daxue Xuebao **22:**373–379.