ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1992, p. 1192–1197
0066-4804/92/061192-06$02.00/0

Vol. 36, No. 6

CI-960, a New Fluoroquinolone, for Therapy of Experimental Ciprofloxacin-Susceptible and -Resistant *Staphylococcus aureus* Endocarditis

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Received 14 January 1992/Accepted 19 March 1992

CI-960 is a new fluoroquinolone with enhanced in vitro activity against gram-positive pathogens. The efficacy of the drug was compared with that of vancomycin by using the rabbit model of nafcillin- and ciprofloxacin-susceptible and -resistant *Staphylococcus aureus* endocarditis. Animals received intravenous therapy with CI-960, 20 mg/kg of body weight every 8 h, or vancomycin, 17.5 mg/kg every 6 h, for 4 days. In a comparison with the effects on untreated controls, both antimicrobial agents effectively cleared bacteremia and significantly reduced bacterial counts in vegetations and tissues of animals infected with any of the test strains. In some cases, the efficacy of CI-960 was superior to that of vancomycin. The therapeutic activity of CI-960 was reduced, but still very good, against ciprofloxacin-resistant strains. One rabbit infected with such a strain and treated with CI-960 was found to harbor a small number of vegetation-associated organisms resistant to the drug at fivefold its original MIC; this was associated with a microbiological, but not a clinical, failure of therapy. We conclude that CI-960 is as effective as vancomycin is in this model of a serious systemic *S. aureus* infection, including that caused by strains resistant to ciprofloxacin. Increases in CI-960 MICs may develop during therapy of infections caused by strains highly resistant to ciprofloxacin, but they appear unlikely to occur in ciprofloxacin-susceptible strains.

CI-960 (AM-1091, PD 127391) is a new fluoroquinolone that has enhanced activity against gram-positive pathogens, including nafcillin-susceptible and -resistant strains of *Staphylococcus aureus* (1, 10). Because of the increased potency of this compound compared with those of older fluoroquinolones, it may retain clinically relevant activity against strains of *S. aureus* that are resistant to such drugs (e.g., ciprofloxacin) (3). In order to examine this possibility, to assess the general in vivo activity of CI-960 against *S. aureus*, and to determine the frequency at which resistance to the drug develops during therapy, we used the rabbit model of endocarditis and nafcillin-susceptible and -resistant, ciprofloxacin-susceptible and -resistant strains of *S. aureus* as test organisms. Alternative therapeutic options for serious staphylococcal infections are needed, especially in light of recent reports of clinically relevant glycopeptide resistance in *Staphylococcus haemolyticus* and *S. aureus* (8, 13). Additionally, if CI-960 is shown to maintain useful activity against strains of *S. aureus* resistant to ciprofloxacin, intravenous or oral therapy of serious infections caused by such organisms might be feasible. Currently, the rather high incidence of fluoroquinolone resistance among methicillin-resistant strains of *S. aureus* at many institutions worldwide eliminates this therapeutic option (4, 11, 12, 15).

MATERIALS AND METHODS

Organisms. The nafcillin-susceptible and -resistant, ciprofloxacin-susceptible strains of *S. aureus* used (SA-1199 and MRSA-494, respectively) were isolated from the bloodstreams of patients with endocarditis. Ciprofloxacin-resistant derivatives of each strain were obtained by passage of SA-1199 and MRSA-494 on gradient plates containing gradually increasing concentrations of ciprofloxacin (2). This produced strains SA-719 and SA-721 (derivatives of SA-1199) and MRSA-732 (derivative of MRSA-494).

In vitro studies. The MICs and MBCs of nafcillin, vancomycin, CI-960, and ciprofloxacin for all strains were determined in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.), which was cation adjusted with calcium and magnesium according to the guidelines of the National Committee for Clinical Laboratory Standards (9). Agar dilution MICs were determined with Mueller-Hinton agar (Difco) (9).

The frequencies at which test strains developed spontaneous mutational resistance to 2-, 5-, and 10-fold the agar dilution CI-960 or ciprofloxacin (for SA-1199 and MRSA-494 only) MICs for the strains were determined by exposing exponential-growth-phase organisms (10^{10} to 10^{11} CFU) to the appropriate concentration of antimicrobial agent incorporated into Mueller-Hinton agar. Colonies were counted 48 h later.

The rate and the extent of the in vitro bactericidal effect of vancomycin and CI-960 against all test strains were determined by time-kill studies. The activity of nafcillin was also evaluated for nafcillin-susceptible strains. Organisms were grown overnight in cation-adjusted Mueller-Hinton broth; this was followed by dilution to ~10^6 CFU/ml with fresh broth prewarmed to 35°C. Nafcillin, vancomycin, or CI-960 was then added to a final concentration of 40, 25, or 3 μg/ml, respectively; these concentrations are similar to those achieved with (or projected for, in the case of CI-960 [see below]) each of the drugs following standard dosing in humans. Cultures were incubated with agitation at 35°C. Parallel cultures containing no antimicrobial agents served

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as controls. Colony counts were determined on a frequent basis by serial dilution and plating techniques. Antibiotic carryover was eliminated by use of a minimum dilution factor of at least 200.

Animal studies. All studies were done by using male New Zealand White rabbits (weight, 2 to 3 kg). Left-sided endocarditis was established as described previously by using an intravenous bacterial inoculum of 10^6 CFU (5). Eighteen hours later, 1 ml of blood for culture was withdrawn from all animals. Serial dilution and plating techniques were used to determine CFU per milliliter of blood. Inclusion in the study required that this blood culture be positive and that the catheter be positioned properly across the aortic valve at the time of autopsy. Rabbits then were randomized to receive 4 days of CI-960 (20 mg/kg of body weight intravenously every 8 h), vancomycin (17.5 mg/kg of body weight intravenously every 6 h), or no treatment (controls). The dose that was administered was adjusted for weight on a daily basis. Controls were sacrificed at the time that therapy was begun in animals receiving antimicrobial agents; this was followed by the determination of bacterial counts in vegetations and tissues (see below).

Serum samples for the measurement of peak (obtained 1 h postdose) and trough (obtained just before a scheduled dose) antibiotic contents were collected from all animals at the time of the first dose on day 3. Blood for culture was also obtained before the first dose on day 3.

Following 4 days of therapy, all animals were sacrificed 8 to 10 h (for vancomycin) or 10 to 12 h (for CI-960) following the final dose and were autopsied in an aseptic manner. Terminal blood cultures and serum samples for the measurement of antibiotic content were obtained; this was followed by removal of vegetations and a 500-mg (mean weight) section of left kidney and spleen for culture. These specimens were weighed, suspended in 0.85% NaCl (final volume, 1 ml), and homogenized. Quantitative bacterial counts, determined by serial dilution and plating techniques, were expressed as the $\log_{10}$ CFU per gram (sensitivity limit, 10 CFU per vegetation or tissue section; culture-negative specimens were considered to contain 10 CFU for numerical and statistical purposes). The effect of antibiotic carryover on cultured material was minimized by the volume of agar used in the culture plates. The dilution effect for cultured material was at least 100-fold.

Antibiotic content of serum. CI-960 concentrations in serum were determined by reversed-phase high-performance liquid chromatography (HPLC). The mobile phase consisted of 21% acetonitrile–79% citric acid (0.05 M)–0.1% ammonium perchlorate–1.154 mM tetrabutylammonium hydroxide. A C18 column (Partisil 5, ODS-3; Whatman International Ltd., Maidstone, United Kingdom) was used at an ambient temperature of 24 to 27°C and a flow rate of 1.2 ml/min. Column effluent was monitored at 340 nM.

HPLC standards were prepared fresh daily. To 200 μl of sample or blank rabbit serum, 50 μl of either HPLC-grade water or CI-960 standard was added. This was followed by the addition of 100 μl of internal standard (PD 118012 [lot R], 8.5 μg/ml; Parke-Davis Pharmaceutical Research, Ann Arbor, Mich.). Precipitation was accomplished by adding 100 μl of acetonitrile-perchloric acid (4:1; vol/vol) to each specimen. The sample or standard was then centrifuged; this was followed by injection of 100 μl of the supernatant onto the column. Retention times for CI-960 and PD 118012 were 7.2 and 10.5 min, respectively. The limit of detection for CI-960 was 0.075 μg/ml, and the standard curve was linear from 0.075 to 5 μg/ml.

TABLE 1. In vitro studies

Test strain and antimicrobial agent	MIC (μg/ml)	MBC (μg/ml)	Mutation frequencies at the following selecting concn[a]:		
			2	5	10
SA-1199					
Nafcillin	0.39	0.39	ND[b]	ND	ND
Vancomycin	0.50	0.50	ND	ND	ND
Ciprofloxacin	0.25	0.25	4.0×10^{-7}	6.2×10^{-10}	$<1 \times 10^{-10}$
CI-960	0.031	0.031	4.6×10^{-8}	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$
SA-719					
Nafcillin	0.39	0.39	ND	ND	ND
Vancomycin	0.78	0.78	ND	ND	ND
Ciprofloxacin	50.0	100.0	ND	ND	ND
CI-960	1.25	2.50	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$
SA-721					
Nafcillin	0.39	0.39	ND	ND	ND
Vancomycin	0.78	0.78	ND	ND	ND
Ciprofloxacin	25.0	50.0	ND	ND	ND
CI-960	0.63	0.63	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$
MRSA-494					
Nafcillin	25.0	100	ND	ND	ND
Vancomycin	0.39	0.39	ND	ND	ND
Ciprofloxacin	0.30	0.60	3.4×10^{-7}	1.4×10^{-9}	2.8×10^{-10}
CI-960	0.031	0.063	1.6×10^{-8}	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$
MRSA-732					
Nafcillin	25.0	100	ND	ND	ND
Vancomycin	0.78	0.78	ND	ND	ND
Ciprofloxacin	50.0	>100	ND	ND	ND
CI-960	1.25	1.25	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$	$<1 \times 10^{-11}$

[a] Multiple of the appropriate agar dilution MIC.
[b] ND, not determined.

Vancomycin concentrations were determined by fluorescence polarization immunoassay (TDx; Abbott Diagnostics, Irving, Tex.) (14). Pooled normal rabbit serum was used to prepare standards and dilute unknowns as needed.

Resistance to CI-960. All isolates recovered from blood, vegetations, or tissues of animals receiving CI-960 were screened for the emergence of resistance to the drug during therapy. This was done by plating undiluted blood and homogenized vegetation and tissue specimens onto Mueller-Hinton agar containing 5- and 10-fold the appropriate agar dilution MIC. Plates were examined for growth 48 h later.

Statistical analysis. Comparisons of blood, vegetation, and tissue bacterial counts were made by one-way analysis of variance; this was followed by Tukey's post hoc test for multiple comparisons. Comparisons of the frequencies of sterilization of blood, vegetations, and renal and splenic tissues were made by use of the Fisher exact test. A P value of <0.05 was considered significant.

RESULTS

In vitro studies. The MICs and MBCs of nafcillin, vancomycin, ciprofloxacin, and CI-960 for each of the test strains are given in Table 1. MICs of CI-960 determined by agar dilution were identical to those given in Table 1 except for MRSA-494; for that strain the agar dilution MIC was 0.063 μg/ml. Similarly, ciprofloxacin agar dilution MICs for SA-1199 and MRSA-494 were equivalent to the broth microdilution values. Frequencies of spontaneous mutational resistance for each test organism to various multiples of its agar

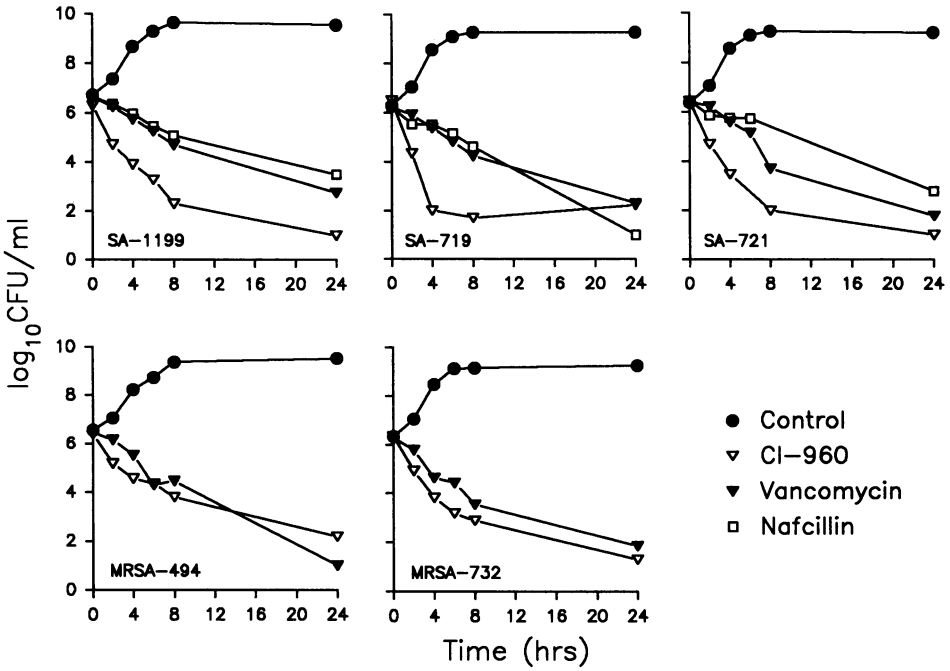

FIG. 1. Time-kill curves for test strains of *S. aureus*. The antimicrobial agent concentrations used were 40, 25, and 3 μg of nafcillin, vancomycin, and CI-960 per ml, respectively.

dilution CI-960 or ciprofloxacin (for SA-1199 and MRSA-494) MIC are also given in Table 1. These frequencies were higher for ciprofloxacin than for CI-960 for both SA-1199 and MRSA-494, with the possible exception of SA-1199 at 10-fold each respective MIC.

Time-kill curves for each test strain are shown in Fig. 1. For all strains, CI-960 produced the most rapid rate of killing during the first 2 h of exposure; over this time period the drug killed each strain more than three times faster than did the other antimicrobial agents. Over an 8-h period, CI-960 killed nafcillin-susceptible strains at nearly twice the rate of vancomycin or nafcillin (0.5 to 0.6 versus 0.2 to 0.3 $\log_{10}$ CFU/ml of reduction per hour, respectively). At the concentrations tested, nafcillin was not more effective than vancomycin against these strains. The slight rise in the number of surviving bacteria between 8 and 24 h for SA-719 exposed to CI-960 was not associated with a rise in the CI-960 MIC for these organisms. For nafcillin-resistant strains, differences in the killing rates produced by CI-960 and vancomycin over the first 8 h were less pronounced; over that time period, CI-960 killed each nafcillin-resistant strain only 30% faster than did vancomycin. By 24 h, differences between the antimicrobial agents were even less pronounced but favored CI-960 for three of the five test strains. Of note was the fact that CI-960 killed ciprofloxacin-susceptible and -resistant strains at comparable rates.

Animal studies. No differences were found in the intensity of pretreatment bacteremia (mean ± standard deviation $\log_{10}$ CFU per milliliter) for animals infected with SA-719 and receiving vancomycin (3.47 ± 1.04) or CI-960 (3.16 ± 1.30) sacrificed after 4 days of therapy or controls sacrificed 18 h after bacterial challenge (3.31 ± 1.17). The same was true for those infected with SA-721 or MRSA-732 and treated with vancomycin (3.81 ± 0.81 and 2.65 ± 0.54, respectively) or CI-960 (3.54 ± 0.52 and 2.48 ± 0.73, respectively) and for controls (3.61 ± 1.26 and 3.27 ± 0.83, respectively). Minor differences in animals infected with SA-1199 and MRSA-494 were noted. Animals infected with either of these test strains and treated with vancomycin had somewhat higher pretreatment bacteremias than were found in those treated with CI-960 (SA-1199, 3.98 ± 0.61 versus 3.30 ± 0.71; MRSA-494, 3.09 ± 0.61 versus 2.47 ± 0.65 [$P < 0.05$ for both comparisons]). The bacteremias of control animals were not different from those of animals infected with either of the strains and randomized to receive antimicrobial agent therapy (SA-1199, 3.54 ± 0.65; MRSA-494, 2.98 ± 0.70).

The peak and trough concentrations in serum achieved with vancomycin and CI-960 are given in Table 2. The peak concentrations of vancomycin were similar to those attainable in humans, whereas those of CI-960 were modestly higher than the anticipated peak concentration of 2 μg/ml (10a). Terminal antimicrobial agent concentrations in serum were, in all cases, lower than the corresponding trough concentrations (data not shown), suggesting that significant drug accumulation did not occur over the 4-day treatment course.

There were no differences in the frequencies of blood culture sterilization during therapy with either antimicrobial agent in animals infected with any of the test strains. Regardless of the infecting organism, 79 to 100% and 94 to 100% of the animals that received vancomycin had sterile cultures after 2 and 4 days, respectively. For those treated with CI-960, the corresponding values were 73 to 100% and 67 to 100%. The lower end of the ranges for animals treated with CI-960 was contributed by animals infected with SA-719, the organism with the lowest susceptibility to the drug with respect to both MIC and MBC.

The quantitative bacterial counts found in vegetations and tissues are given in Table 3. Compared with control animals, significant reductions in these counts were noted at each cultured site in rabbits treated with either drug ($P < 0.01$ for all comparisons). With respect to reductions in renal or

TABLE 2. Antimicrobial agent concentrations in serum

Infecting strain and treatment	Concn (μg/ml) in serum[a]	
	Peak	Trough
SA-1199		
Vancomycin	31.1 ± 5.8	4.0 ± 1.8
CI-960	3.32 ± 0.5	0.10 ± 0.02
SA-719		
Vancomycin	23.2 ± 3.6	1.7 ± 1.0
CI-960	4.12 ± 0.85	0.15 ± 0.07
SA-721		
Vancomycin	26.1 ± 5.0	2.3 ± 1.4
CI-960	3.24 ± 0.89	0.09 ± 0.04
MRSA-494		
Vancomycin	24.9 ± 4.4	3.0 ± 1.6
CI-960	3.86 ± 0.71	0.15 ± 0.09
MRSA-732		
Vancomycin	25.4 ± 3.8	2.2 ± 1.0
CI-960	4.04 ± 0.71	0.15 ± 0.05

[a] Values are means ± standard deviations.

splenic bacterial counts, there were no differences between groups of animals that received either vancomycin or CI-960. However, reductions in bacterial counts in vegetations favored the use of CI-960 for animals infected with SA-1199 and SA-721 ($P < 0.01$ for both). Both drugs produced a similar proportion of culture-negative vegetations and tissues for all infecting organisms.

Resistance to CI-960. Isolates of SA-719 able to grow on agar containing fivefold the CI-960 MIC for the organism were recovered from the vegetation material of 1 of 15 (7%) animals that received the drug. Resistance at this level was verified by determining the MIC for each isolate. In this single animal, residual vegetation and tissue bacterial counts were approximately 2 $\log_{10}$ CFU/g higher than those in most other rabbits in the same treatment group. However, resistant organisms made up only 3.95×10^{-5}% of the organisms recovered from vegetations.

No resistant organisms were recovered from animals treated with CI-960 and infected with any of the other test strains.

DISCUSSION

Numerous studies have shown that fluoroquinolones such as ciprofloxacin and ofloxacin compare favorably with standard therapy in animals with experimental *S. aureus* infections (5–7). However, none of those studies examined the effect of decreasing the susceptibility of the test organism on drug efficacy. Such investigations were impractical in the earlier studies (5–7); for drugs like ciprofloxacin and ofloxacin, the peak serum concentration-to-MIC ratios are not high enough to allow for more than modest rises in MICs. However, because of the increased potency of CI-960, significant rises in MICs can be tolerated and can leave the drug with reasonable therapeutic activity. The results of the present study indicate that the efficacy of CI-960 compares favorably with that of vancomycin over an MIC range of 0.031 to 1.25 μg/ml, a 40-fold rise, and a corresponding decrease in peak serum concentration-to-MIC ratios from more than 100 to 3 to 5. Residual vegetation bacterial counts did rise as the CI-960 MIC rose, but the only significant difference noted was that between SA-719 and SA-1199 (6.05 ± 2.66 versus 4.13 ± 1.78 $\log_{10}$ CFU/g of vegetation; $P < 0.05$). However, in all cases CI-960 performed as well as or better than vancomycin, even though serum vancomycin levels were at least twofold above the MIC throughout the dosing interval for all test strains.

TABLE 3. Vegetation and tissue bacterial counts

Infecting strain and treatment	No. of rabbits	Bacterial counts ($\log_{10}$ CFU/g) in[a]:		
		Vegetation	Kidney	Spleen
SA-1199				
Vancomycin	14	7.00 ± 1.78 (0)	1.18 ± 0.05 (13)	1.26 ± 0.16 (12)
CI-960	16	4.13 ± 1.38 (4)	1.11 ± 0.08 (16)	1.25 ± 0.16 (15)
None (control)	11	9.92 ± 0.85 (0)	4.66 ± 0.97 (0)	5.88 ± 0.49 (0)
SA-719				
Vancomycin	16	6.79 ± 2.52 (1)	1.43 ± 0.50 (12)	1.50 ± 0.79 (12)
CI-960	15	6.05 ± 2.66 (2)	1.98 ± 1.35 (10)	2.19 ± 1.63 (10)
None (control)	9	9.70 ± 0.53 (0)	4.84 ± 1.04 (0)	5.74 ± 0.61 (0)
SA-721				
Vancomycin	16	7.10 ± 2.28 (0)	1.27 ± 0.29 (13)	1.32 ± 0.44 (14)
CI-960	15	4.73 ± 1.92 (1)	1.17 ± 0.08 (15)	1.25 ± 0.17 (14)
None (control)	10	9.40 ± 0.77 (0)	5.18 ± 1.37 (0)	5.89 ± 0.73 (0)
MRSA-494				
Vancomycin	18	2.98 ± 1.58 (13)	1.25 ± 0.53 (17)	1.53 ± 0.76 (16)
CI-960	15	2.50 ± 0.32 (14)	1.12 ± 0.12 (15)	1.25 ± 0.08 (15)
None (control)	11	8.45 ± 1.12 (0)	5.41 ± 1.55 (0)	5.26 ± 0.83 (0)
MRSA-732				
Vancomycin	10	3.26 ± 1.97 (6)	1.18 ± 0.07 (10)	1.42 ± 0.58 (9)
CI-960	9	4.13 ± 2.24 (3)	1.45 ± 0.74 (8)	1.68 ± 0.88 (7)
None (control)	7	8.64 ± 0.87 (0)	4.89 ± 0.92 (0)	5.22 ± 0.79 (0)

[a] Values are means ± standard deviations. Values in parentheses are numbers of culture-negative ("sterile") specimens.

Pretreatment bacteremias were somewhat higher for animals infected with SA-1199 and MRSA-494 and treated with vancomycin than they were for those treated with CI-960. It is likely that these differences would have disappeared with larger numbers of animals. However, the possibility that a higher degree of pretreatment bacteremia represents a larger starting bacterial load cannot be excluded, and the effect(s) of this difference on the outcome of therapy is not known.

Vancomycin and CI-960 cleared bacteremias at equivalent rates. Additionally, both drugs were effective in reducing bacterial counts in vegetations and tissues, as determined by comparison with the counts in untreated controls. Both drugs were equivalent with respect to reducing renal and splenic bacterial counts, and a greater reduction in vegetation bacterial counts for rabbits infected with SA-1199 and SA-721 was achieved with CI-960. These data, combined with our findings and those of others showing low frequencies of spontaneous single-step mutation to resistance to the drug, suggest that CI-960 might be a viable therapeutic option for treatment of serious *S. aureus* infections in humans (3). However, one rabbit infected with SA-719 was found to harbor a small number of vegetation-associated organisms that were resistant at fivefold the CI-960 MIC. Because of the extremely small number of such organisms that were recovered, the microbiological failure of therapy in this rabbit cannot be attributed to drug resistance. However, that resistance developed at all during such a short treatment course raises some concern about the possibility of this phenomenon occurring during therapy of serious human infections in which the bacterial load is as high as it was in our model. This may be of greater concern during therapy of infections caused by strains, such as SA-719, that have borderline susceptibilities to the drug and, thus, a relatively low peak serum concentration-to-MIC ratio. This ratio was 3 for SA-719, in comparison with a value of 107 for the parent strain, SA-1199.

The peak concentrations of CI-960 achieved in rabbit serum in the present study exceeded those projected for human serum (2 μg/ml). It is possible that diminished efficacy may have resulted if our peak concentrations in serum had been nearer to this value, especially with respect to the ciprofloxacin-resistant strains. Toxicity may limit the peak concentrations of CI-960 achievable in serum; human toxicology and pharmacokinetic studies need to be performed to define reasonable dosage regimens and the maximal safe peak concentrations of the drug.

Time-kill studies demonstrated that vancomycin is as active as nafcillin against the nafcillin-susceptible strains that we used. Nafcillin generally is the drug of first choice for serious human infections caused by strains of *S. aureus* susceptible to the drug. However, in individuals intolerant to β-lactam antibiotics, vancomycin is the accepted alternative. On the basis of this fact and our in vitro data, our use of vancomycin as standard therapy to which CI-960 was compared is validated.

Vancomycin reduced bacterial counts in vegetations to a lesser degree in nafcillin-susceptible strains than it did in nafcillin-resistant strains ($P < 0.01$). We have observed this phenomenon previously (5–7). Rabbits infected with SA-1199 or its derivatives had higher pretreatment vegetation bacterial counts than did animals infected with MRSA-494 or MRSA-732 ($P < 0.01$; see data for control rabbits in Table 3). This increased bacterial load may be an important contributing factor to the reduced efficacy that we observed.

Recently, there have been a number of reports from various institutions throughout the world of a high incidence of fluoroquinolone resistance among *S. aureus* isolates, especially methicillin-resistant strains (4, 11, 12, 15). Vancomycin remains active against such organisms, but if glycopeptide resistance were to become common in *S. aureus*, the therapeutic options for such a strain that was also fluoroquinolone resistant would be limited. CI-960 may be a viable alternative, but the efficacy of the drug in infections caused by strains for which the ciprofloxacin MICs are even higher than those that we evaluated needs to be assessed.

In conclusion, we found CI-960 to be equivalent to vancomycin in a model of a serious *S. aureus* infection, regardless of the nafcillin or ciprofloxacin susceptibility of the test strain. This drug may serve as an alternative to vancomycin for use in humans with similar infections, but the possibility of the emergence of resistance during therapy cannot be ignored. This is especially true for therapy of infections caused by strains with borderline susceptibilities to the drug. Additional work is needed to establish the clinical relevance of this phenomenon, especially in infections caused by highly ciprofloxacin-resistant strains.

ACKNOWLEDGMENT

This work was supported by a grant from Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Mich.

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