β -Lactams versus Glycopeptides in Treatment of Subcutaneous Abscesses Infected with *Staphylococcus aureus*

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The antibacterial efficacies of the β -lactam antibiotics nafcillin and cefazolin were compared with those of the glycopeptide antibiotics vancomycin and teicoplanin in rats with subcutaneous abscesses infected with methicillin-susceptible *Staphylococcus aureus*. Animals were treated with antibiotics or diluent for 3 or 7 days. Rats receiving any antibiotic treatment, with the exception of teicoplanin-treated animals at day 7, had lower bacterial counts in their abscesses than did controls at days 3 and 7. Rats in the nafcillin and cefazolin treatment groups had lower bacterial counts in their abscesses than did rats in the vancomycin and teicoplanin treatment groups at days 3 and 7. The β -lactam antibiotics were more effective therapy than the glycopeptide antibiotics in rats with subcutaneous abscesses infected with methicillin-susceptible *S. aureus*. In vitro, animal, and clinical data comparing β -lactam and glycopeptide treatment of *S. aureus* infections were reviewed along with the resulting treatment recommendations.

There is increasing clinical evidence that vancomycin or teicoplanin may be less effective than a penicillinase-resistant penicillin in the treatment of serious infections, such as endocarditis, caused by *Staphylococcus aureus* (10, 22, 23, 27). This clinical evidence is supported by in vitro and animal studies showing the inferior performances of glycopeptides compared with those of β -lactams (6, 7, 27). In the study described here, we compared the in vivo efficacies of the β -lactam antibiotics nafcillin and cefazolin with those of the glycopeptide antibiotics vancomycin and teicoplanin in a standardized animal test system of subcutaneous abscesses infected with methicillin-susceptible *S. aureus* (MSSA).

MATERIALS AND METHODS

Experimental animals. Fifty male Fisher 344 rats (weight, approximately 200 g; Charles River Breeding Laboratories, Inc., Wilmington, Mass.) were housed in standard cages and were observed for 1 week prior to treatment randomization. Rats were allowed free access to a standardized diet (rat chow; Purina, St. Louis, Mo.) and water. Animals were weighed daily, with antibiotic doses adjusted to the rat's weight on each day.

Bacterial strain and in vitro testing. The MSSA strain used was ATCC 29213. The MIC and MBC were determined by standard dilution methods in cation-adjusted Mueller-Hinton broth (24), but at an initial inoculum of 10^7 CFU/ml (the same inoculum used in the subcutaneous abscess). The MBC was also determined by similar methods in 90% heat-inactivated pooled human serum. The MIC in serum could not be determined because of the turbidity of the medium. Time-kill curve (TKC) studies were performed by standard methods in either cation-adjusted Mueller-Hinton broth or 90% heat-inactivated pooled human serum. The initial inoculum for the TKC studies was also 10^7 CFU/ml, and all antibiotics were present at 20 μ g/ml. Inocula for all in vitro studies consisted of

logarithmic-phase bacteria. The published quality control ranges of MICs for this strain of *S. aureus* when tested by standard in vitro methods (24) are as follows: nafcillin, 0.12 to 0.5 μ g/ml; cefazolin, 0.25 to 1.0 μ g/ml; vancomycin, 0.5 to 2.0 μ g/ml; and teicoplanin, 0.25 to 1.0 μ g/ml (25).

Abscess induction and antibiotic treatment. The model of a *Bacteroides fragilis*-infected subcutaneous abscess in mice described by Joiner et al. (18) was adapted as described previously (29, 30). Animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (30 mg/kg of body weight), and the left flank was shaved with electric clippers. Abscesses were induced by the subcutaneous injection of approximately $7 \log_{10}$ CFU of MSSA in a slurry of autoclaved cecal contents and Mueller-Hinton broth with a final volume of 1.0 ml. The bacterial inoculum in the abscess consisted of logarithmic-phase organisms. Antibiotic treatment began within 1 h of abscess induction. Animals were treated in groups of five rats each for either 3 or 7 days. The dosage regimens for the antibiotics were selected in an attempt to produce concentrations in serum relevant to the concentrations achievable in human serum. All antibiotics were administered twice daily by the subcutaneous route. Nafcillin (Wyeth-Ayerst Laboratories, Philadelphia, Pa.) was administered at 200 mg/kg, cefazolin (Eli Lilly & Co., Indianapolis, Ind.) was administered at 100 mg/kg, vancomycin (Eli Lilly & Co.) was administered at 100 mg/kg, and teicoplanin (Marion Merrell Dow, Inc., Kansas City, Mo.) was administered at 200 mg/kg. Vancomycin and teicoplanin were both administered as a double loading dose at the first administration. Control rats received diluent twice daily.

Serum antibiotic concentrations. Serum antibiotic concentrations were drawn at the time that peak levels were achieved (1 h) and at 6 h following administration of the final dose prior to sacrifice. Peak levels were determined to occur 1 h after injection by preliminary studies which revealed a broad plateau peak concentration centered at about this time. Trough antibiotic concentrations could not be reliably measured because of the limited sensitivity of the antibiotic assay. Blood was obtained from the tail vein. Antibiotic concentrations in serum were determined by a disk diffusion bioassay by using *S. aureus* ATCC 20213. Standard curves were made with antibiotic in pooled rat serum. The disk diffusion bioassay was performed

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TABLE 1. In vitro susceptibility of *S. aureus* ATCC 29213

Antibiotic	MIC breakpoint ($\mu\text{g/ml}$) ^a	Broth		MBC ($\mu\text{g/ml}$) in 90% serum
		MIC ($\mu\text{g/ml}$)	MBC ($\mu\text{g/ml}$)	
Nafcillin	2.0	1.0	1.0	8.0
Cefazolin	8.0	1.0	1.0	2.0
Vancomycin	4.0	2.0	4.0	4.0
Teicoplanin	8.0	2.0	2.0	8.0

^a Data were obtained from reference 25.

with 20 μl of serum from antibiotic-treated animals or standard solution. Standard curves were generated by linear regression. Samples with unknown concentrations of drug in serum were calculated from the equation of the line. The lower limits of detection for the antibiotics were as follows: nafcillin, 13 $\mu\text{g/ml}$; cefazolin, 5 $\mu\text{g/ml}$; vancomycin, 8 $\mu\text{g/ml}$; and teicoplanin, 4 $\mu\text{g/ml}$.

Abscess microbiology. Bacterial counts in the abscesses were quantitated at the end of 3 or 7 days of therapy. Rats were sacrificed in CO_2 . Abscesses were dissected free of the rats and were homogenized in 3.0 ml of iced normal saline. Serial dilutions in saline were plated in duplicate for counting. The dilutional effect prior to plating made significant antibiotic carryover unlikely. Results were expressed as the total number of organisms per abscess. It was not possible to measure the antibiotic concentrations in the abscesses.

Statistics. Antibiotic concentrations in serum are expressed as the means and ranges. Antibiotic concentrations in serum on day 3 and day 7 were compared by the unpaired Student *t* test. Bacterial counts in the abscesses are expressed as the mean $\pm$ 1 standard deviation. Comparisons between treatment groups was performed by analysis of variance with the post hoc Tukey multiple comparisons test. Tests were two-sided, with significance set at *P* values of ≤ 0.05 .

RESULTS

In vitro testing. Despite the higher than usual inoculum, the MSSA test isolate remained susceptible to all antibiotics used, as reflected by broth dilution MICs below the approved breakpoints (Table 1). The broth dilution MBCs were not increased relative to the corresponding MICs and were also below the MIC breakpoint of each antibiotic. The MBCs in serum increased only modestly relative to the corresponding broth dilution values for nafcillin (three tube dilutions) and teicoplanin (two tube dilutions). Results of TKC studies were nearly identical whether they were performed in broth or serum. All antibiotics demonstrated gradual cidal activity, with greater than 3-log₁₀-unit killing by 24 h in either broth or serum.

Serum antibiotic concentrations. Because there were no statistically significant differences between serum antibiotic concentrations at day 3 or 7 of therapy, results for the two treatment periods were pooled (Table 2). All peak serum antibiotic concentrations approximated those obtainable in a clinical setting. On the basis of the levels of drug in serum obtained 6 h following administration of the dose, serum antibiotic concentrations exceeded the MIC for the MSSA for the majority of the 12-h dosing interval. Because of the broad peak plateau and the long half-life of teicoplanin, the 6-h postdose concentration was not substantially different from the concentration measured at 1 h.

Abscess microbiology. The initial inoculum of MSSA at the time of abscess induction was 7.16 log₁₀ CFU. After 3 days of

TABLE 2. Serum antibiotic concentrations

Antibiotic	Mean (range) concn ($\mu\text{g/ml}$)	
	Peak	6 h postdose
Nafcillin	63 (47–79)	— ^a
Cefazolin	91 (71–102)	11 (7–18)
Vancomycin	44 (25–74)	20 (11–29)
Teicoplanin	44 (30–66)	46 (30–66)

^a The concentration of nafcillin in the serum of five animals was 15 $\mu\text{g/ml}$ and was below the limit of detection of 13 $\mu\text{g/ml}$ in the serum of five animals.

treatment, all animals treated with antibiotics had statistically lower bacterial counts compared with the counts in control animals (Table 3). Cefazolin was more effective than any of the other antibiotic treatments at reducing bacterial counts, and nafcillin was more effective than either vancomycin or teicoplanin, which were equally effective. After 7 days of treatment, animals treated with cefazolin, nafcillin, and vancomycin had lower bacterial counts than control animals, while those treated with teicoplanin did not. Cefazolin and nafcillin treatments were more effective in reducing bacterial counts than vancomycin and teicoplanin treatments. Vancomycin treatment was more effective than teicoplanin treatment in reducing the bacterial counts in the abscesses.

DISCUSSION

In the subcutaneous abscess test system described here, β -lactam antibiotics demonstrated greater bactericidal activity than glycopeptide antibiotics against MSSA. The superiority of nafcillin and cefazolin over vancomycin and teicoplanin was not likely due to the advantageous concentrations of the β -lactams in serum because all profiles of antibiotic concentrations in serum approximated clinically achievable levels. Nafcillin, cefazolin, and teicoplanin are all $>85\%$ protein bound, whereas vancomycin is $<50\%$ protein bound. Although a high degree of protein binding has been shown to adversely affect antimicrobial activity and extravascular penetration (2, 13), differential protein binding is insufficient to explain the enhanced activities of the β -lactams in the system. Nafcillin and, to a lesser extent, teicoplanin were adversely affected by the presence of serum on the basis of the MBCs in serum compared with those in broth. These effects were less than would be predicted by the high degree of protein binding of these antibiotics. In addition, the TKCs obtained by using a mid-dosing interval concentration of 20 $\mu\text{g/ml}$ for all antibiot-

TABLE 3. Influence of antibiotic treatment regimen on CFU of *S. aureus* in subcutaneous abscesses

Treatment group	Log ₁₀ CFU/abscess (mean $\pm$ SD)	
	3-day treatment ^a	7-day treatment ^b
Control	9.23 $\pm$ 0.37	8.82 $\pm$ 0.50
Nafcillin	3.49 $\pm$ 0.65	3.63 $\pm$ 0.55
Cefazolin	2.48 $\pm$ 0.67	3.50 $\pm$ 0.46
Vancomycin	7.94 $\pm$ 0.29	6.17 $\pm$ 1.16
Teicoplanin	7.71 $\pm$ 0.31	7.64 $\pm$ 0.55

^a At 3 days: control versus all antibiotic regimens, *P* < 0.01; nafcillin or cefazolin regimen versus vancomycin or teicoplanin regimen, *P* < 0.001; cefazolin versus nafcillin regimen, *P* < 0.05.^b At 7 days: control versus vancomycin, nafcillin, or cefazolin regimen, *P* < 0.001; nafcillin or cefazolin regimen versus vancomycin or teicoplanin regimen, *P* < 0.001; vancomycin versus teicoplanin regimen, *P* < 0.05.

ics failed to reveal a significant adverse effect of serum on the cidal activity of any of the antibiotics. Other investigators have demonstrated a greater adverse effect from protein binding on the killing activity of teicoplanin than on the killing activity of vancomycin (1). Differences between in vivo and in vitro conditions, including protein binding, other influences of plasma proteins, or bacterial growth phase within the abscess, may have contributed to the superiority of the β -lactams in the test system. These variables were not addressed in the present investigation.

The clinical importance of high degrees of antibiotic protein binding has rarely been demonstrated. Chambers and colleagues (8) reported that the highly protein bound cephalosporin cefonicid failed to clear cultures of blood from three of four patients with *S. aureus* endocarditis, by 5 days, despite apparently adequate levels of drug in serum. Protein binding may also be relevant to the glycopeptide antibiotic teicoplanin. Two European trials (4, 15) and a U.S. trial (16) in which relatively low doses of teicoplanin were used to treat infections caused by *S. aureus* were terminated because of poor efficacy. Inadequate concentrations of free teicoplanin, particularly at the time of the trough concentration, were cited as the most likely explanation for the therapeutic failures. Inherent differences in antibacterial activity between the glycopeptide and β -lactam antibiotics were generally not considered. Subsequent clinical trials of teicoplanin for the treatment of *S. aureus* endocarditis in the United States used substantially higher doses than did the earlier trials. Results of those trials have not yet been published. It has previously been shown that the rate of cidal activity of the β -lactam antibiotics may be more rapid than the rate of cidal activity of the glycopeptide antibiotics (7, 27). The clinical significance of this finding is not known, and this difference in cidal rates was not demonstrated in the present study. Although of debatable clinical significance (17, 20, 26), tolerance was not demonstrated with any of the treatment antibiotics used in the present study and was unlikely to have contributed to the in vivo results.

The observed superiority of the β -lactam antibiotics may be due to differences in penetration into the abscesses or differences in the activities of the antibiotics in the abscess environment. It is not possible to comment directly on antibiotic penetration to the site of infection, since the antibiotic concentrations in the abscesses could not be measured in the present study. However, it has been reported previously (12) that teicoplanin diffusion into cardiac vegetations is suboptimal and less than that of the β -lactam antibiotic penicillin. Teicoplanin was concentrated at the periphery of the vegetation, whereas penicillin penetrated to the center of the vegetation and was concentrated to a lesser extent at the periphery. Similar data on vancomycin are not available. The β -lactam antibiotics may be more active in the abscess environment of low pH, low O_2 tension, etc. It has been reported that both nafcillin and vancomycin retain their activities under these conditions, although their activities are diminished with a high inoculum (3).

Although cefazolin was more active than nafcillin at day 3 of therapy and vancomycin was more effective than teicoplanin at day 7 of therapy, these differences between antibiotics of the same class were much less striking than the differences observed between the β -lactam and the glycopeptide antibiotics observed at both day 3 and day 7 of therapy. The significance of these results is uncertain.

The majority of previously reported studies in animals have concluded that glycopeptide antibiotics are equal in efficacy to β -lactam antibiotics but may be less rapidly bactericidal. In a rat model of *S. aureus* endocarditis, Cantoni et al. (5, 6)

investigated in two studies the activity of vancomycin versus that of cloxacillin or amoxicillin-clavulanate. Vancomycin was found to be as effective as either cloxacillin or amoxicillin-clavulanate but appeared to be less rapidly bactericidal. Chambers and Sande (9) found teicoplanin to be as effective as nafcillin in a rabbit model of *S. aureus* endocarditis. Chambers and Kennedy (7), using a rabbit model of streptococcal endocarditis, found teicoplanin to be less rapidly bactericidal than penicillin. Data from studies in animals, the present report, and previously published studies must be extrapolated with great care because of differences between those studies and the clinical setting. Differences could include bacterial inocula, timing of antibiotic therapy, bacteriologic endpoint, or innumerable additional factors.

Clinical reports supporting the possibility that β -lactam antibiotics may be more effective than glycopeptide antibiotics in treating infections caused by MSSA lend more importance to this claim. Earlier clinical reports on the activity of vancomycin in treating infections caused by *S. aureus* concluded that vancomycin is as effective as β -lactam antibiotics (11, 28). Those studies were retrospective with historical controls and included few or no patients with documented endocarditis treated with vancomycin. More recently, several studies have compared the duration of bacteremia or outcome in patients with *S. aureus* endocarditis treated with vancomycin regimens with the same parameters in subjects historically treated with nafcillin-based regimens. Korzeniowski et al. (21) published results for both drug addicts and non-drug addicts with *S. aureus* endocarditis treated with nafcillin or nafcillin and gentamicin. Non-drug addicts treated with nafcillin or nafcillin and gentamicin had mean durations of bacteremia of 4.1 and 2.8 days, respectively, and successful outcomes were obtained in 82 and 84% of subjects, respectively. Drug addicts treated with nafcillin or nafcillin and gentamicin had mean durations of bacteremia of 3.4 and 2.9 days, respectively, and successful outcomes were obtained in 100 and 96% of episodes, respectively. Studies reporting the duration of bacteremia and outcomes in patients with *S. aureus* endocarditis treated with vancomycin-based treatment regimens have not been comparative and have exclusively involved populations of drug addicts. The results of those studies may be compared with the data for drug addicts reported by Korzeniowski et al. (21). Levine et al. (22) reported results for 19 drug addicts with methicillin-resistant *S. aureus* endocarditis treated with vancomycin with or without rifampin or an aminoglycoside. The mean duration of bacteremia was not reported; however, the median duration of 6 days was twice as long as the median duration of 3 days reported by Korzeniowski et al. (21). The success rate for treatment was substantially lower (68%) (22). Small and Chambers (27) reported on their experience in treating 13 drug addicts with *S. aureus* endocarditis with vancomycin-based regimens. The duration of bacteremia was not included in the report; however, the success rate of only 62% was strikingly less than the 96 to 100% success rate reported with nafcillin-based regimens. Most recently, Levine and colleagues (23) published results of a study in which 42 drug addicts with endocarditis caused by methicillin-resistant *S. aureus* were treated with either vancomycin or vancomycin and rifampin. The mean duration of bacteremia in these patients was 9 days, and there was no difference between the two study groups. There were few complications related to the sustained bacteremias, and the success rate was 86%.

Although not definitive, in vitro, animal, and clinical data suggest that β -lactam antibiotics may be more effective than glycopeptides in treating infections caused by MSSA. Until more substantial clinical data become available, it would seem

prudent to avoid using glycopeptides out of convenience when treating infections caused by MSSA and to fully evaluate patients with a history of a β -lactam allergy prior to discarding the class of antibiotics (19). The prescription of vancomycin, which has increased significantly in the last decade (14), should be made in the setting of *S. aureus* infection when dictated by susceptibility test results or substantiated allergy or intolerance.

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