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In Vitro Antistaphylococcal Activity of Pefloxacin Alone and in Combination with Other Antistaphylococcal Drugs

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MICs of pefloxacin and nine antistaphylococcal drugs were determined for 200 isolates of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, and *Staphylococcus saprophyticus*. All the strains were susceptible to pefloxacin, vancomycin, and rifampin. Oxacillin-resistant strains were uniformly resistant to cephalothin and were more likely to be resistant to gentamicin, erythromycin, clindamycin, doxycycline, and trimethoprim-sulfamethoxazole than were oxacillin-susceptible strains. Time-kill studies with 23 strains of *S. aureus*, *S. epidermidis*, and *S. haemolyticus* indicated that the relative order of bactericidal activities was gentamicin ≥ pefloxacin > oxacillin > vancomycin > rifampin. Pefloxacin combined with oxacillin or vancomycin killed staphylococci more rapidly than oxacillin or vancomycin alone but less rapidly than pefloxacin alone. Gentamicin combined with oxacillin, vancomycin, or pefloxacin resulted in the most rapid killing of gentamicin-susceptible strains. Rifampin combined with oxacillin, vancomycin, or pefloxacin reduced the bactericidal activities of those drugs, but rifampin resistance was not observed as it was with rifampin alone. Pefloxacin is a potentially useful antistaphylococcal agent.

Despite the availability of numerous antistaphylococcal drugs, the treatment of severe staphylococcal infections remains a major therapeutic challenge. A new class of antimicrobial agents, the fluoroquinolones, is under development. These drugs are consistently active against both methicillin- or oxacillin-susceptible (OS) and methicillin- or oxacillin-resistant (OR) staphylococci (2, 8, 9, 20, 26). In this study, we compared the in vitro antistaphylococcal activity of one fluoroquinolone, pefloxacin, alone and in combination with other drugs, with the antistaphylococcal activities of other drugs and drug combinations.

MATERIALS AND METHODS

Organisms. Staphylococci were clinical isolates identified by using a profile of 27 biochemical tests and the interpretive criteria of Kloos and Schleifer (13). Included were 50 strains each of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus haemolyticus* and 25 strains each of *Staphylococcus hominis* and *Staphylococcus saprophyticus*. Half of the *S. aureus*, *S. epidermidis*, and *S. haemolyticus* strains and all of the *S. hominis* and *S. saprophyticus* strains were OS; the others were OR.

MICs. Laboratory standards of oxacillin, cephalothin, pefloxacin, vancomycin, gentamicin, erythromycin, clindamycin, doxycycline, and trimethoprim-sulfamethoxazole were supplied by the manufacturers, diluted according to instructions, and dispensed into microdilution plates using an MIC-2000 Plus dispensing machine (Dynatech Laboratories, Inc., Alexandria, Va.) in $\log_2$ dilution steps within the range of 0.06 to 64 μg/ml. MICs were determined by a standardized microdilution method (18) in 0.1-ml volumes of cation-supplemented Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.). For oxacillin and cephalothin, 2% NaCl was added to the medium (18). Trimethoprim-sulfamethoxazole was tested in a fixed 1:19 ratio; 0.1 U of thymidine phosphorylase (Burroughs Wellcome Co., Research Triangle Park, N.C.) per ml was added. The final inoculum was ca. 5×10^5 CFU/ml. The trays were incubated at 35°C. MIC endpoints were determined at 18 h; oxacillin susceptibility or resistance was determined by using appropriate breakpoints for the various species tested (9).

To screen for synergy or antagonism, MICs were determined for 10 strains each of OS *S. aureus*, OR *S. aureus*, OS *S. epidermidis*, OR *S. epidermidis*, OS *S. haemolyticus*, and OR *S. haemolyticus* by using fixed 1:1 (by weight) drug combinations: oxacillin with pefloxacin, gentamicin, or rifampin against OS strains; vancomycin with pefloxacin, gentamicin, or rifampin against OR strains; and pefloxacin with gentamicin or rifampin against all strains.

Killing kinetics. Killing-kinetic studies were performed with pefloxacin, oxacillin, vancomycin, rifampin, gentamicin, and various combinations of those drugs with 23 strains of *S. aureus*, *S. epidermidis*, and *S. haemolyticus*. Studies were performed in 50-ml volumes of cation-supplemented Mueller-Hinton broth with an inoculum of ca. 10^6 CFU/ml. Antibiotic concentrations were selected to represent those observed in vivo and to be fourfold or greater than the MICs for susceptible organisms. For the individual drugs, concentrations tested and respective MICs for study strains were: pefloxacin, 4 μg/ml and 0.13 to 1 μg/ml; oxacillin, 16 μg/ml and 0.13 to 0.5 μg/ml; vancomycin, 8 μg/ml and 0.5 to 2 μg/ml; rifampin, 1 and ≤0.06 μg/ml; gentamicin, 4 μg/ml and ≤0.13 or ≥2 μg/ml. Incubation was at 35°C in a shaker water bath. Quantitative subcultures were performed after 0, 6, and 24 h of incubation to determine CFU per milliliter. At those times, 0.1-ml volumes of undiluted and serially diluted 1:10 portions were dispersed into 6-ml Mueller-Hinton agar pour plates. Antimicrobial dilution was 1:600 in the 10^{-2} plate, which ensured that a fourfold or greater $\log_{10}$ reduction in CFU per milliliter could be detected for all drug-organism combinations despite antibiotic carry-over. The plates were incubated at 35°C for 48 h before the colonies were counted.

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TABLE 1. In vitro susceptibilities of staphylococci to antimicrobial agents with unimodal distributions of MICs[a]

Organism (25 strains of each)	MIC (μg/ml)[b]											
	Oxacillin			Cephalothin			Pefloxacin			Vancomycin		
	Range	50%	90%	Range	50%	90%	Range	50%	90%	Range	50%	90%
S. aureus, OS	0.25–2	0.5	2	0.5–2	0.5	2	0.13–1	0.25	0.5	≤0.25–1	0.5	1
S. aureus, OR	>16	>16	>16	16–>32	>32	32	0.25–0.5	0.5	0.5	≤0.25–2	0.5	1
S. epidermidis, OS	≤0.13–0.25	≤0.13	0.25	≤0.25	≤0.25	≤0.25	0.25–1	0.5	1	0.5–2	1	2
S. epidermidis, OR	1–>16	>16	>16	0.5–4	2	4	0.25–1	0.5	0.5	1–2	2	2
S. haemolyticus, OS	≤0.13–1	0.25	0.5	≤0.25–0.5	≤0.25	0.5	0.25–1	0.5	0.5	≤0.25–1	0.5	1
S. haemolyticus, OR	>16	>16	>16	2–>32	>32	>32	0.25–1	0.5	0.5	0.5–4	1	2
S. hominis	≤0.13–1	≤0.13	0.5	≤0.25–0.5	≤0.25	≤0.25	0.25–1	0.5	1	0.5–1	0.5	1
S. saprophyticus	0.25–2	1	1	≤0.25–1	1	1	1–4	4	4	0.5–2	1	1

[a] Rifampin MICs were ≤0.06 μg/ml for all strains.
[b] 50% and 90%, MICs for 50 and 90% of strains, respectively.

RESULTS

MICs. The susceptibilities of staphylococci to oxacillin, cephalothin, pefloxacin, vancomycin, and rifampin are shown in Table 1. For each species, there was a typical unimodal distribution of oxacillin and cephalothin MICs for OS and OR strains. Pefloxacin, vancomycin, and rifampin were equally active against OS and OR strains and also had unimodal distributions of MICs.

The susceptibilities of staphylococci to gentamicin, erythromycin, clindamycin, doxycycline, and trimethoprim-sulfamethoxazole are shown in Table 2. The distribution of MICs for these drugs was usually bimodal, although some organisms were uniformly susceptible to some drugs. In all instances, OR strains were more likely to be resistant to these drugs than were OS strains.

All eight drug combinations were indifferent in inhibitory activity against 55 of the 60 strains tested. For five strains of OR (MICs, >16 μg/ml), gentamicin-resistant (MICs, ≥8 μg/ml) staphylococci (one *S. aureus* strain, three *S. epidermidis* strains, and one *S. haemolyticus* strain), there was synergy between oxacillin and gentamicin; all the strains were inhibited by 2 to 4 μg of both drugs per ml in combination.

Killing kinetics. The killing effects of various drugs and drug combinations with staphylococci are shown in Table 3; consistent results were observed for each drug-organism combination. The following generalizations, with minor species variations, can be derived from the results shown in Table 3. (i) The relative order of bactericidal activity against susceptible strains of *S. aureus* was gentamicin = pefloxacin > oxacillin > vancomycin > rifampin; for *S. epidermidis* and *S. haemolyticus*, it was gentamicin > pefloxacin > oxacillin > vancomycin > rifampin. With 7 of the 23 strains (2 OS *S. aureus* strains, 1 OR *S. aureus* strain, 1 OS *S. epidermidis* strain, 2 OS *S. haemolyticus* strains, and 1 OR *S. haemolyticus* strain), there was breakthrough growth from 6 to 24 h of incubation with rifampin; MICs increased from ≤0.06 to >8 μg/ml. (ii) Pefloxacin killed all three species of staphylococci with similar rapidity; the relative rates of killing for the other drugs were *S. epidermidis* > *S. haemolyticus* > *S. aureus*. (iii) Pefloxacin combined with oxacillin or vancomycin killed staphylococci more rapidly than oxacillin or vancomycin alone but less rapidly than pefloxacin alone. (iv) Gentamicin combined with oxacillin or vancomycin resulted in enhanced killing of *S. aureus* compared with each drug alone; these were the most rapidly bactericidal combinations of drugs against gentamicin-susceptible (MICs, ≤0.25 μg/ml) strains. Gentamicin combined with pefloxacin also resulted in rapid killing. Against *S. epidermidis* and *S. haemolyticus*, gentamicin combined with oxacillin, vancomycin, or pefloxacin resulted in rapid killing, but synergy could not be detected because of the marked bactericidal activity of gentamicin alone. Against gentamicin-resistant (MICs, ≥2 μg/ml) strains of all three species, these drug combinations were indifferent. (v) Rifampin combined with oxacillin, vancomycin, or pefloxacin reduced their bactericidal activities against all three species, but the emergence of rifampin resistance was not observed.

DISCUSSION

Among the various species of staphylococci, *S. aureus* and *S. epidermidis* have received the greatest attention as significant pathogens. The antistaphylococcal penicillins, such as oxacillin, are considered the drugs of choice for treating infections caused by these organisms, most of which produce penicillinase (9). In penicillin-allergic patients,

TABLE 2. In vitro susceptibilities of staphylococci to antimicrobial agents with nonunimodal distributions of MICs

Organism (25 strains of each)	% Susceptible to antimicrobial agent at indicated concn (μg/ml)											
	Gentamicin			Erythromycin		Clindamycin		Doxycycline			TMP-SMZ[a]		
	≤0.25	2–4	≥8	≤0.25	≥8	≤0.25	≥8	≤0.5	1–4	≥8	≤4	8–32	≥64
S. aureus, OS	92	0	8	92	8	96	4	92	0	8	100	0	0
S. aureus, OR	68	4	28	8	92	48	52	40	4	56	96	0	4
S. epidermidis, OS	100	0	0	88	12	96	4	72	12	16	96	4	0
S. epidermidis, OR	20	32	48	12	88	12	88	24	52	24	84	0	16
S. haemolyticus, OS	96	4	0	84	16	100	0	68	8	24	76	20	4
S. haemolyticus, OR	16	24	60	4	96	56	44	0	64	36	4	32	64
S. hominis	100	0	0	84	16	92	8	44	8	48	88	8	4
S. saprophyticus	100	0	0	88	12	100	0	96	0	4	100	0	0

[a] TMP-SMZ, Trimethoprim-sulfamethoxazole.

TABLE 3. Killing of staphylococci after incubation with antimicrobial agents alone and in combination

Antimicrobial agent(s)	Mean decrease in CFU (log_{10})/ml from baseline for organism at indicated time											
	OS *S. aureus* (n = 4)		OR *S. aureus* (n = 4)		OS *S. epidermidis* (n = 3)		OR *S. epidermidis* (n = 5)		OS *S. haemolyticus* (n = 3)		OR *S. haemolyticus* (n = 3)	
	6 h	24 h	6 h	24 h	6 h	24 h	6 h	24 h	6 h	24 h	6 h	24 h
Control	(2.1)[a]	(3.1)	(2.1)	(2.9)	(2.1)	(2.7)	(1.8)	(2.9)	(1.7)	(2.6)	(2.0)	(2.8)
Oxacillin	1.0	2.3	NT[b]	NT	2.3	>4	NT	NT	1.7	>4	NT	NT
Vancomycin	NT	NT	0.3	2.9	NT	NT	1.4	3.2	NT	NT	0.5	3.4
Pefloxacin	2.9	3.3	2.9	3.8	2.6	>4	2.5	3.8	3.4	>4	2.9	3.5
Gentamicin[c]	2.6	>4	2.2	>4	>4	>4	>4	>4	>4	>4	>4	>4
	(1.8)	(3.2)	(0.7)	(2.6)	NT	NT	(1.0)	(2.8)	NT	NT	(0.5)	(3.1)
Rifampin[d]	0.5	0.8	0.3	0.9	1.6	>4	1.6	2.6	0.8	1.6	0.9	1.5
Oxacillin-pefloxacin	1.4	3.1	NT	NT	3.2	>4	NT	NT	2.4	>4	NT	NT
Vancomycin-pefloxacin	NT	NT	0.8	3.6	NT	NT	2.1	3.8	NT	NT	1.1	>4
Oxacillin-gentamicin[c]	>4	>4	NT	NT	>4	>4	NT	NT	>4	>4	NT	NT
	0.9	2.1	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Vancomycin-gentamicin[c]	NT	NT	3.9	>4	NT	NT	>4	>4	NT	NT	>4	>4
	NT	NT	0.5	3.0	NT	NT	1.2	3.9	NT	NT	1.0	3.0
Pefloxacin-gentamicin[c]	3.1	>4	2.6	>4	>4	>4	>4	>4	>4	>4	>4	>4
	1.9	3.2	1.7	>4	NT	NT	1.8	3.6	NT	NT	2.3	3.4
Oxacillin-rifampin	0.3	0.5	NT	NT	1.0	2.0	NT	NT	0.4	1.0	NT	NT
Vancomycin-rifampin	NT	NT	0.3	0.7	NT	NT	0.5	1.0	NT	NT	1.1	1.9
Pefloxacin-rifampin	0.4	1.3	0.4	1.1	1.4	3.2	1.8	2.9	1.2	1.9	1.0	1.8

[a] Numbers in parentheses represent increases in CFU per milliliter.
[b] NT, Not tested.
[c] Strains which were susceptible to gentamicin are indicated in row 1, and strains which were resistant to gentamicin are indicated in row 2.
[d] Strains which developed resistance during incubation with rifampin are excluded from 24-h values (see the text).

cephalothin and vancomycin are appropriate substitutes. For infections caused by OR strains, vancomycin is considered the treatment of choice (4, 12, 15, 24). Because none of these drugs is uniformly efficacious in difficult-to-eradicate infections such as endocarditis, it has become common practice to add an aminoglycoside, such as gentamicin, or rifampin. The rationale for adding gentamicin is based on observed in vitro synergy (17, 19, 25), enhanced reduction of bacteria in experimentally induced endocardial vegetations in rabbits (17, 19), and the results of some studies which indicated improved efficacy in patients with endocarditis (12, 14, 15). The addition of rifampin has also been justified based on improved efficacy despite frequently observed in vitro antagonism (1, 3, 12, 15, 24). In vitro, the major benefit of adding rifampin to penicillins or vancomycin has been a reduction in the emergence of rifampin resistance; unfortunately, this has not been a consistent observation in vivo (1, 3, 7). It has been postulated that the favorable clinical results observed with rifampin combinations are due to the ability of rifampin to concentrate within phagocytic cells and kill intracellular staphylococci (16). Resistance to the fluoroquinolones has also been observed during treatment of patients with difficult-to-eradicate staphylococcal infections (5, 10), and these drugs, like rifampin, are concentrated in human neutrophils where they are lethal to staphylococci (6).

The fluoroquinolones have been consistently active in vitro against the most common species of clinically significant staphylococci. Unlike most other antistaphylococcal drugs, they were equally active against OS and OR strains (2, 8, 9, 20, 26). In this study, pefloxacin killed *S. aureus* strains as rapidly as gentamicin and more rapidly than oxacillin, vancomycin, or rifampin. It killed *S. epidermidis* and *S. haemolyticus* strains less rapidly than gentamicin but more rapidly than oxacillin, vancomycin, or rifampin. Although oxacillin, vancomycin, and rifampin had various degrees of bactericidal activity against the three species (*S. epidermidis* > *S. haemolyticus* > *S. aureus*), the bactericidal activity of pefloxacin was the same for all species. In general, gentamicin enhanced the bactericidal activity of pefloxacin, oxacillin, and vancomycin (against gentamicin-susceptible strains), rifampin tended to antagonize those drugs, and combinations of pefloxacin with oxacillin or vancomycin resulted in killing intermediate to that observed with the individual drugs. Combination MICs were inadequate to detect these drug interactions.

Other studies with fluoroquinolones and *S. aureus* have had similar results. Ciprofloxacin was more rapidly bactericidal than vancomycin (2, 20) or rifampin (2), ciprofloxacin plus gentamicin or amikacin was often synergistic (21), ciprofloxacin plus rifampin was antagonistic when the concentration of either drug was higher than the MIC (22), and ciprofloxacin plus vancomycin was not more bactericidal than ciprofloxacin alone (20). When sera spiked with ciprofloxacin, pefloxacin, nafcillin, or vancomycin were tested for bactericidal activity against OS *S. aureus*, the fluoroquinolones were more rapidly bactericidal than nafcillin or vancomycin. The bactericidal activity of these sera was reduced by the addition of rifampin; this antagonism was also reflected in reduced serum bactericidal titers with nafcillin but not vancomycin, ciprofloxacin, or pefloxacin (11). When postinfusion sera from volunteers given intravenous pefloxacin, amikacin, or both were tested for bactericidal activity against OS *S. aureus*, amikacin was more bactericidal than pefloxacin; the combination usually had intermediate activity when compared with the individual drugs. Serum inhibitory and bactericidal titers for the three regimens were essentially the same. When OR *S. aureus* was tested, results were somewhat different, but it was unclear whether the strains tested were amikacin susceptible or amikacin resistant (23).

The results of this study indicate that pefloxacin is a potentially useful antistaphylococcal drug. When treating

infections caused by OS or OR strains of *S. aureus*, *S. epidermidis* or *S. haemolyticus*, combinations with aminoglycosides or rifampin are reasonable for testing clinical efficacy, based on reasoning analogous to that used for combinations of oxacillin or vancomycin with those drugs.

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