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In Vitro Activity of Rifampin in Combination with Oxacillin Against *Staphylococcus aureus*

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The in vitro activity of rifampin alone and in combination with oxacillin was determined for 75 *Staphylococcus aureus* strains (64 susceptible and 11 resistant to oxacillin). Minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) were determined by broth microdilution; antibiotic combinations were evaluated by microdilution checkerboard and time-kill studies. The 90% MIC of rifampin was ≤0.015 μg/ml after both 24 and 48 h of incubation. The 90% MBC of rifampin was ≤2.0 μg/ml on subculture at 24 h of incubation and ≤0.5 μg/ml on subculture at 48 h. MIC checkerboards with oxacillin-susceptible strains revealed an additive or indifferent effect in 35 strains (55%) and antagonism in 29 strains (45%). MBC checkerboards performed by subculture at 24 h demonstrated antagonism for all but one of the oxacillin-susceptible strains, with sub-MBCs of rifampin impairing the bactericidal activity of oxacillin. MBC checkerboards performed by 48-h subculture revealed antagonism with 37 strains (58%); in 26 additional strains (40%), a synergistic, additive, or indifferent effect was observed at low antibiotic concentrations, but antagonism was seen at higher concentrations. Time-kill studies tended to show indifference rather than antagonism with oxacillin plus rifampin. In checkerboards performed with oxacillin-resistant strains, the addition of rifampin did not improve oxacillin inhibitory or bactericidal activity to a clinically significant extent; however, the addition of oxacillin improved the bactericidal activity of rifampin at easily achievable serum concentrations.

Rifampin in combination with other antibiotics, including semisynthetic penicillins, vancomycin, and gentamicin, has been advocated for treatment of serious staphylococcal infections unresponsive to conventional single-drug therapy (2, 5, 7, 12, 14, 16). It has been noted that rifampin has impressive in vitro inhibitory activity against staphylococci (1, 10, 18, 23), reaches potentially therapeutic concentrations in a wide range of tissue and body fluids (including cerebrospinal fluid) (3, 20, 21), and kills bacteria sequestered within leukocytes (13). Rifampin-resistant staphylococci emerge rapidly when rifampin is used alone, necessitating the administration of an additional antibiotic with antistaphylococcal activity (4, 10, 12).

Although the use of rifampin in combination with other agents is buttressed by persuasive theoretical considerations as well as by in vitro and animal model experiments (12, 16) and anecdotal clinical reports (2, 5, 7, 14), some studies have suggested that the bactericidal activity of rifampin against staphylococci is not as impressive as its inhibitory activity (10, 25). Moreover, when rifampin has been combined with β-lactam antibiotics (26) or vancomycin (24), antagonism has been noted by some investigators. Previous studies have examined relatively few strains and used various methodologies, which may account for the conflicting data in the literature. To clarify this situation, we studied the activity of oxacillin plus rifampin against a large number of clinical isolates of *Staphylococcus aureus* with standard checkerboard and time-kill techniques. We found that this combination has limited, although potentially useful, bactericidal activity against a large number of clinical strains of *S. aureus*.

MATERIALS AND METHODS

Bacterial strains. The combination of oxacillin plus rifampin was tested with 64 oxacillin-susceptible and 11 oxacillin-resistant clinical isolates of *S. aureus*. Oxacillin resistance was defined as a minimal inhibitory concentration (MIC) of ≤2.0 μg/ml after 48 h of incubation; strains with an MIC of ≤2.0 μg/ml were considered susceptible (15). The 48-h incubation time was selected to enhance detection of oxacillin resistance (22). All oxacillin-susceptible strains were isolated from patients at the Children's Hospital Medical Center, Boston, Mass. Oxacillin-resistant strains were

kindly supplied by Donald Craven, Boston City Hospital, Boston, Mass.; Adolf Karchmer, Massachusetts General Hospital, Boston; James Allen, Centers for Disease Control, Atlanta, Ga.; and Leon Sabath, University of Minnesota, Minneapolis. Strains were preserved at −60°C until tested.

Antibiotics. Oxacillin sodium was supplied by Beecham Laboratories, Bristol, Tenn. Stock solutions were prepared in distilled water and stored at −60°C. Rifampin was supplied by Dow Chemical Co., Indianapolis, Ind. Rifampin was reconstituted in methanol and diluted to working concentrations with distilled water; dilutions were used on the day of preparation.

MICs and MBCs and checkerboards. Broth microdilution plates were prepared with an automated system (MIC-2000; Dynatech Laboratories, Inc., Alexandria, Va.) which dispensed 0.1-ml samples of twofold macrotube dilutions of oxacillin and rifampin in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with 50 mg of Ca^{2+} and 25 mg of Mg^{2+} per liter. Oxacillin concentrations in MIC and checkerboard microtiter plates ranged from 16.0 to 0.03 and 2.0 to 0.03 μg/ml, respectively. Rifampin concentrations in both plates ranged from 2.0 to 0.002 μg/ml. Microtiter plates were stored at −60°C. The following strains were included with each run of susceptibility and checkerboard tests for quality control purposes: *S. aureus* ATCC 25923 and ATCC 29213, *Streptococcus faecalis* ATCC 29212, and group B streptococci CDC 76-014749 and 78-089149.

Inocula were prepared by adjusting a 2- to 4-h Mueller-Hinton broth culture to approximately 10^8 CFU/ml with a nephelometer (Biovation Inoculum Reader; Biovation Inc., Richmond, Calif.) and diluting to 10^7 CFU/ml with sterile water. Each well of the MIC and checkerboard microdilution plates was then inoculated with 0.0015 ml of this suspension, using a 96-prong automated inoculator (Dynatech Laboratories). Thus, the final inoculum was approximately 1.5×10^5 CFU/ml. Inoculated plates were covered and incubated for 48 h at 35°C.

MICs were interpreted at 24 and 48 h as the minimum concentration of antibiotic which completely inhibited growth. Minimal bactericidal concentrations (MBCs) were performed by subculturing from the microdilution plates after 24 and 48 h of incubation with a 10-μl Eppendorf pipette (Brinkman Instruments, Westbury, N.Y.). Thus, MBC endpoints represented an approximately 99.9% kill. Microdilution plates were agitated manually, and the contents of the wells were mixed with the pipette tips before subculture. Subcultures were plated onto 150-mm Mueller-Hinton agar plates (Scott Laboratories, Inc., Fiskville, R.I.).

Checkerboard tests were interpreted by modifications of standard criteria (9, 23) as follows: synergy, ≥2 tube dilution decrease in the MIC (MBC) of both drugs; additive effect, 1 to 2 tube dilution decrease in the MIC (MBC) of one drug and a 1 tube dilution decrease in the MIC (MBC) of the other drug; indifferent effect, 1 tube dilution decrease in the MIC (MBC) of one drug and no change in the MIC (MBC) of the other drug or no change in the MIC (MBC) of either drug; antagonism, increase in the MIC (MBC) of either or both drugs.

Time-kill studies. Time-kill studies were performed in cation-supplemented Mueller-Hinton broth by the method of Krogstad and Moellering (9). Subcultures were performed for colony counts on Mueller-Hinton agar at 0, 6, 24, and 48 h. Four oxacillin-susceptible *S. aureus* strains were studied. These specific strains were chosen because we had observed antagonism with these strains at therapeutic levels of rifampin and oxacillin on checkerboard testing and wanted to confirm this potentially important observation with another methodology. Antibiotic concentrations tested included the rifampin MBC plus either the oxacillin MBC or 10 times the oxacillin MBC. The high concentration of oxacillin was included to simulate clinically achievable antibiotic levels. The following definitions were used: synergy, ≥100-fold increase in killing with the combination of drugs as compared with the most effective single agent; additive or indifferent effect, <100-fold increase or decrease in killing or no difference in killing with the combination as compared with the most effective single agent; antagonism, ≥100-fold decrease in killing with the combination as compared with the most effective single agent.

RESULTS

Inhibitory and bactericidal activity. All of the 64 oxacillin-susceptible strains had oxacillin MICs of ≤0.5 μg/ml after 24 h of incubation. None of these strains exhibited tolerance to oxacillin (17); MBCs for all strains were ≤1 μg/ml after 24 h of incubation (Table 1). A very slight increase in MICs and MBCs was noted by extending the incubation time to 48 h. All but

TABLE 1. In vitro inhibitory and bactericidal activity of oxacillin against 75 *S. aureus* strains

Type of strain (no.) and time (h) of incubation	MIC (μg/ml)[a]			MBC (μg/ml)[b]		
	Range	50%	90%	Range	50%	90%
Oxacillin susceptible (64)						
24	0.25–0.5	0.25	0.5	0.25–1.0	0.5	1.0
48	0.25–1.0	0.5	0.5	0.25–1.0	0.5	1.0
Oxacillin resistant (11)						
24	4.0–>16.0	16.0	>16.0	>16.0	>16.0	>16.0
48	8.0–>16.0	>16.0	>16.0	>16.0	>16.0	>16.0

[a] 50% and 90%, MICs of antibiotic required to inhibit 50 and 90% of strains, respectively.
[b] 50% and 90%, MBCs of antibiotic required to kill 50 and 90% of strains, respectively.

TABLE 2. In vitro inhibitory and bactericidal activity of rifampin against 75 *S. aureus* strains

Type of strain (no.) and time (h) of incubation	MIC (μg/ml)[a]			MBC (μg/ml)[b]		
	Range	50%	90%	Range	50%	90%
Oxacillin susceptible (64)						
24	0.004–0.03	0.008	0.015	0.03–>2.0	1.0	2.0
48	0.004–0.125	0.015	0.015	0.008–1.0	0.015	0.5
Oxacillin resistant (11)						
24	0.004–0.015	0.015	0.015	2.0–>2.0	2.0	>2.0
48	0.008–0.03	0.015	0.015	0.125–1.0	0.5	1.0

[a] 50% and 90%, MICs of antibiotic required to inhibit 50 and 90% of strains, respectively.
[b] 50% and 90%, MBCs of antibiotic required to kill 50 and 90% of strains, respectively.

one of the 11 oxacillin-resistant staphylococci had oxacillin MICs and MBCs of ≥16 μg/ml at 48 h. The additional 24 h of incubation resulted in a 1 to 2 tube dilution increase in the MICs of two strains, but these strains had MICs which were within the resistant range even at 24 h.

All 75 strains of staphylococci were extremely susceptible to rifampin by MIC testing (Table 2). MBCs were considerably higher than MICs when subcultures were performed after 24 h of incubation (Table 2), with a 90% MBC of ≤2.0 μg/ml. The rifampin MBC was at least 32 tube dilutions greater than the MIC in 56 of 64 (88%) oxacillin-susceptible strains and in all 11 of the oxacillin-resistant strains. Improved bactericidal activity was observed when subcultures were performed after 48 h of incubation; the 90% MBC for rifampin fell to ≤0.5 μg/ml, and the MBC/MIC ratio was ≥32 for only 16% of the oxacillin-susceptible strains and 82% of the oxacillin-resistant strains. All strains were killed by concentrations of rifampin which are easily achieved in serum with standard oral dosages (8).

TABLE 3. Checkerboard MICs and MBCs for 64 oxacillin-susceptible *S. aureus* strains

Effect	No. (%) of strains		
	24-h MIC	MBC	
		24 h	48 h
Synergy	0 (0)	0 (0)	0 (0)
Additive	25 (39)	0 (0)	1 (2)
Indifferent	10 (16)	0 (0)	0 (0)
Antagonism	29 (45)	64 (100)[a]	63 (98)[b]

[a] In one strain (2%), an additive effect was seen at low rifampin and oxacillin concentrations, but antagonism was observed at higher concentrations.
[b] In 18 strains (28%), an additive or indifferent effect was seen at low rifampin and oxacillin concentrations, but antagonism was observed at higher concentrations. In 8 strains (12%), synergy was seen at low concentrations, whereas antagonism was observed at higher concentrations.

Checkerboard testing. MIC checkerboard testing with oxacillin-susceptible strains revealed an additive effect in 25 (39%), an indifferent effect in 10 (16%), and antagonism in 29 (45%) (Table 3). MBC checkerboards showed antagonism with all of the oxacillin-susceptible strains when subcultures were performed after 24 h of incubation. For 50 of the 64 strains (78%), there was little or no impact on killing by rifampin with changes in the concentration of oxacillin, but sub-MBC concentrations of rifampin apparently antagonized the bactericidal activity of oxacillin (representative checkerboard, Fig. 1). When subcultures were performed after 48 h of incubation, antagonism was observed with all but one of the oxacillin-susceptible strains. In 26 of the strains (40%), a synergistic, additive, or indifferent effect was seen at low antibiotic concentrations, but antagonism was seen at higher concentrations (Table 3; representative checkerboard, Fig. 2). This effect is consistent with a hetero-additive isobol for homodynamic drugs described by Loewe (11). The improved bactericidal activity of rifampin at 48 h was evident in the presence of low concentrations of oxacillin. Staphylococci isolated on a 48-h subculture of

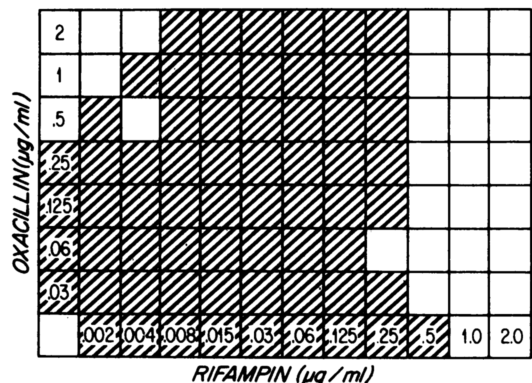

FIG. 1. Checkerboard MBC at 24 h of incubation of strains SA1. ▨, Growth.

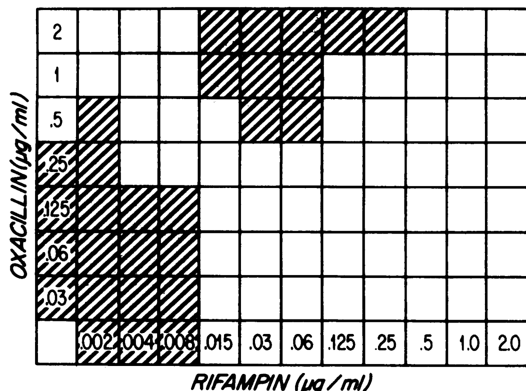

FIG. 2. Checkerboard MBC at 48 h of incubation of strains SA2. ▨, Growth.

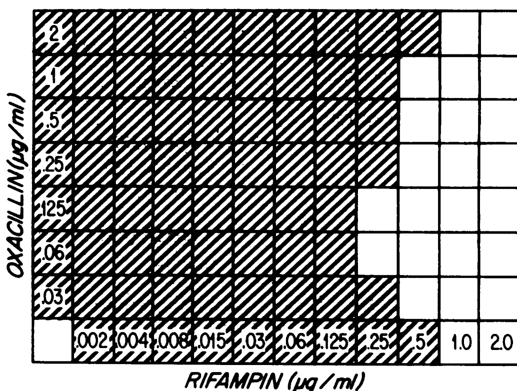

FIG. 3. Checkerboard MBC at 48 h of incubation of strain R2021. ▨, Growth.

wells containing the rifampin MBC and an oxacillin concentration greater than the oxacillin MBC had not changed in their susceptibilities to either oxacillin or rifampin alone.

It was not possible to accurately classify the results of checkerboard testing with oxacillin-resistant strains, since oxacillin concentrations in the microdilution plates were not high enough to detect a 2 tube dilution reduction in oxacillin MICs and MBCs. However, in no case did the addition of rifampin at concentrations less than the rifampin MIC inhibit growth of staphylococci in wells containing ≤ 2 μg of oxacillin per ml, the breakpoint for oxacillin susceptibility. In addition, sub-MBCs of rifampin did not produce killing in wells containing 2 μg of oxacillin per ml (Fig. 3). Oxacillin produced no change in the inhibitory activity of rifampin but did improve rifampin bactericidal activity by 1 to 2 tube dilutions (Fig. 3).

Time-kill studies. The combination of rifampin and oxacillin at their MBCs produced an indifferent effect with oxacillin-susceptible *S. aureus* strains. When the rifampin MBC was combined with oxacillin at 10 times its MBC, killing was not as rapid as with oxacillin alone (representative study, Fig. 4). However, this effect on killing was not sufficient to satisfy the criterion for antagonism.

DISCUSSION

The combination of rifampin plus a bactericidal cell wall-active antibiotic has produced striking improvement in some patients with serious staphylococcal disease (2, 5, 14), but clinical experience with this antibiotic combination has been limited. In vitro studies have suggested that rifampin is not bactericidal for gram-positive cocci and may impair the bactericidal effect of other agents.

The studies of Sabath et al. (18) are often cited as demonstrating the antistaphylococcal effects of rifampin, but only MICs were performed by these investigators. Kunin et al. (10) noted low MICs with very small inocula of *S. aureus*, but much higher MICs and numerous "skip tubes" with inocula of 10^5 to 10^6 CFU; MBCs were not reported, but time-kill curves showed no bactericidal activity for three of the eight strains examined. Excellent bactericidal activity was noted against *S. aureus* by Tuazon et al. (23) and

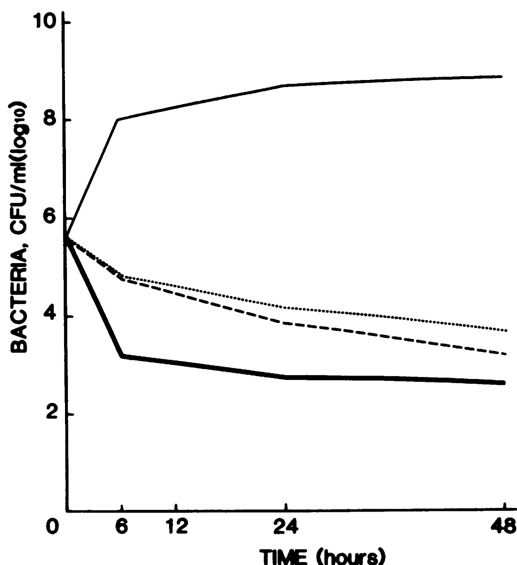

FIG. 4. Time-kill study of strain SA10 tested with an oxacillin concentration (5 μg/ml) 10 times greater than the oxacillin MBC and a rifampin concentration (1.0 μg/ml) equal to the rifampin MBC. ———, Oxacillin at 5.0 μg/ml; – – –, rifampin at 1.0 μg/ml; · · ·, oxacillin at 5.0 μg/ml plus rifampin at 1.0 μg/ml; ———, control.

against *Staphylococcus epidermidis* by Archer (1), but Zinner et al. (25) found that MBCs for both *S. aureus* and *S. epidermidis* were much higher than MICs when microtiter plates were vigorously agitated before subculturing. Although Tuazon and colleagues (23) noted synergy against some *S. aureus* strains with rifampin and nafcillin, partial synergy, indifference, or antagonism were observed with most strains. Zinner et al. (26) observed some synergy against *S. aureus* and *S. epidermidis* with low concentrations of rifampin and methicillin in MIC checkerboards, but there was antagonism in MBC checkerboards. Time-kill studies revealed synergy at low antibiotic concentrations but antagonism at higher concentrations. Sande and Johnson (19) found antagonism with rifampin and penicillin in both time-kill studies and a rabbit model of staphylococcal endocarditis. Rifampin in combination with vancomycin has shown antagonism against *S. aureus* in checkerboard studies and indifference or antagonism in time-kill experiments (24). We recently reported antagonism of rifampin and penicillin against group B streptococci, particularly with antibiotic concentrations likely to be achieved in patients (M. Maduri Traczewski, E. G. Szymczak, and D. A. Goldmann, Rev. Infect. Dis., in press).

In the present study, all *S. aureus* strains were inhibited by very low concentrations of rifampin, but killing required higher concentrations. For the majority of strains, the rifampin MBC was at least 32-fold greater than the MIC. However, most strains were killed by concentrations of rifampin well below peak achievable serum levels (8).

MIC checkerboards demonstrated an additive or indifferent effect for most strains and antagonism for the remainder; synergy was not observed. Antagonism was generally observed in MBC checkerboards when subcultures were performed at either 24 or 48 h. Examination of the MBC checkerboards revealed that sub-MBCs of rifampin nullified the bactericidal activity of oxacillin. On the other hand, killing was achieved by rifampin concentrations near the MBC, regardless of the concentration of oxacillin present in the microdilution wells. The mechanism of the antagonism we observed is unknown, but it is likely that rifampin concentrations which are sufficient to inhibit bacterial cell growth but not to kill staphylococci interfere with the bactericidal effect of cell wall agents like oxacillin which act on growing bacteria (6).

As discouraging as these in vitro results may seem, they in no way imply that rifampin in combination with oxacillin would be ineffective therapy for serious staphylococcal disease. Although rifampin antagonized the bactericidal activity of oxacillin, the majority of strains were killed in the presence of oxacillin by rifampin concentrations achievable in serum. Moreover, oxacillin would be expected to prevent outgrowth of rifampin-resistant subpopulations when treating infections associated with higher concentrations of staphylococci (12). In addition, rifampin penetrates tissues exceptionally well (20) and can kill staphylococci sequestered within leukocytes (13); these are potentially important therapeutic advantages which were not addressed by our studies. In view of our findings, however, clinical evaluation of rifampin and oxacillin for the treatment of *S. aureus* infections should proceed with caution.

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