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# Antipneumococcal Activities of Cefpirome and Cefotaxime, Alone and in Combination with Vancomycin and Teicoplanin, Determined by Checkerboard and Time-Kill Methods

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**The checkerboard titration method was used to test the synergy of cefpirome and cefotaxime with teicoplanin or vancomycin against 35 penicillin-susceptible, 34 penicillin-intermediate, and 31 penicillin-resistant pneumococci. The MICs at which 50 and 90% of isolates are inhibited ($MIC_{50}$s and $MIC_{90}$s, respectively) of both cefpirome and cefotaxime were 0.016 and 0.06 μg/ml, respectively, for penicillin-susceptible strains and 0.125 and 0.5 μg/ml, respectively, for penicillin-intermediate strains. The $MIC_{50}$s and $MIC_{90}$s of cefotaxime for penicillin-resistant strains were 1.0 and 2.0 μg/ml, respectively, and those of cefpirome were 0.5 and 1.0 μg/ml, respectively. All pneumococci were inhibited by cefpirome at MICs of ≤1.0 μg/ml. The $MIC_{50}$s and $MIC_{90}$s of vancomycin and teicoplanin (0.25 and 0.25 μg/ml and 0.03 and 0.03 μg/ml, respectively) did not differ for the three groups. Checkerboard synergy studies showed that cefpirome and vancomycin showed synergy for 31 strains (fractional inhibitory concentration [FIC] indices, ≤0.5) cefpirome and teicoplanin showed synergy for 18 strains, cefotaxime and vancomycin showed synergy for 51 strains, and cefotaxime and teicoplanin showed synergy for 27 strains. Cefpirome and vancomycin had FIC indices indicating indifference (2.0) for two strains, and cefotaxime and vancomycin had FIC indices indicating indifference for one strain. All other FIC indices indicating indifference or additivity were >0.5 to 1.0. No FIC indices indicating antagonism (>4.0) were found. Synergy between β-lactams and glycopeptides for three susceptible, three intermediate, and three resistant strains were tested by the time-kill assay, and all combinations were synergistic by this method. Synergy between cephalosporins and glycopeptides can be demonstrated and may be useful for the treatment of pneumococcal infections, especially meningitis.**

The worldwide incidence of infections caused by pneumococci resistant to penicillin G and other antimicrobial agents has increased at an alarming rate during the past two decades and in particular in the past 5 years. The main foci of penicillin-resistant pneumococci are South Africa, Spain, and eastern Europe (1). In the United States recent surveys have shown an increase in the rate of resistance to penicillin from <5% before 1989 (including <0.02% of isolates for which MICs are ≥2.0 μg/ml) to 6.6% in 1991 and 1992 (MICs of ≥2.0 μg/ml for 1.3% of isolates) (3, 22). A recent report from metropolitan Atlanta has documented an overall pneumococcal penicillin resistance rate of 25% during 1994; 7% of strains were highly resistant, and a high percentage were also resistant to other agents (10). The problem of resistant pneumococci is exacerbated by their tendency to spread from area to area and from country to country (14, 15).

Current regimens for the treatment of pneumococcal infections are mainly based on historical data and studies performed with patients infected with fully susceptible strains. However, the emergence of strains of *Streptococcus pneumoniae* resistant to penicillin, and often resistant to other classes of antimicrobial agents as well, complicates empiric treatment of pneumococcal infections, especially meningitis and otitis media (6–8, 11, 19).

Cefotaxime and ceftriaxone, alone or in combination with vancomycin, form the mainstay of therapy for serious systemic infections (including meningitis) caused by penicillin-intermediate and penicillin-resistant pneumococci (6–8, 11, 19). Previous studies have shown that the cefpirome MICs for these strains are usually 1 dilution lower than those of cefotaxime and ceftriaxone (2, 5, 8, 21). Additionally, the modal MICs of teicoplanin for all pneumococcal strains are 0.06 μg/ml, compared with 0.25 μg/ml for vancomycin (9, 20).

In order to shed further light on this situation, the present study evaluated the in vitro activities of cefotaxime, cefpirome, teicoplanin, vancomycin and a combination of each β-lactam and each glycopeptide by the checkerboard broth microdilution titration method against 100 penicillin-susceptible and penicillin-resistant strains. Time-kill curves were also used to study the interaction of these combinations against nine strains with various penicillin susceptibilities.

## MATERIALS AND METHODS

**Bacterial strains.** One hundred pneumococci were studied. These comprised 35 penicillin-susceptible (MICs, ≤0.06 μg/ml), 34 penicillin-intermediate (MICs, 0.125 to 1.0 μg/ml), and 31 penicillin-resistant (MICs, ≥2.0 μg/ml) strains. The organisms were frozen at −70°C until use and were subcultured onto 5% sheep blood agar plates (BBL Microbiology Systems, Detroit, Mich.) prior to use.

**Antimicrobial agents.** Cefpirome and cefotaxime were obtained from Roussel Uclaf (Paris, France), vancomycin was obtained from Eli Lilly & Co. (Indianapolis, Ind.), and teicoplanin was obtained from Marion Merrell Dow AG (Horgen, Switzerland).

**MIC determinations and synergy testing.** MIC determinations and synergy testing were performed by the checkerboard method in microtiter trays with cation-supplemented Mueller-Hinton broth (Difco) with 5% lysed horse blood (Cleveland Scientific, Inc., Bath, Ohio) (4). Cefpirome and cefotaxime were tested at 11 concentrations (from 0.004 to 4.0 μg/ml), vancomycin was tested at 7 concentrations (from 0.03 to 2.0 μg/ml), and teicoplanin was tested at 7 concentrations (from 0.004 to 0.25 μg/ml). The trays were prepared with a 96-channel dispenser and were stored at −70°C until use. Cefotaxime or cefpirome was dispensed alone in the first row, and each drug was combined with vancomycin or teicoplanin in the remaining rows. Vancomycin or teicoplanin was

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TABLE 1. MICs of individual antimicrobial agents

| Antimicrobial agent and strain[a] | MIC (μg/ml) | | |
|---|---|---|---|
| | Range | 50% | 90% |
| Penicillin G | | | |
| Penicillin-S | 0.008–0.06 | 0.016 | 0.06 |
| Penicillin-I | 0.125–1.0 | 0.25 | 1.0 |
| Penicillin-R | 2.0–8.0 | 2.0 | 4.0 |
| Cefotaxime | | | |
| Penicillin-S | 0.016–0.25 | 0.016 | 0.06 |
| Penicillin-I | 0.03–1.0 | 0.125 | 0.5 |
| Penicillin-R | 0.5–2.0 | 1.0 | 2.0 |
| Cefpirome | | | |
| Penicillin-S | 0.016–0.125 | 0.016 | 0.06 |
| Penicillin-I | 0.03–1.0 | 0.125 | 0.5 |
| Penicillin-R | 0.25–1.0 | 0.5 | 1.0 |
| Vancomycin | | | |
| Penicillin-S | 0.125–0.25 | 0.25 | 0.25 |
| Penicillin-I | 0.125–0.5 | 0.25 | 0.25 |
| Penicillin-R | 0.06–0.25 | 0.125 | 0.25 |
| Teicoplanin | | | |
| Penicillin-S | 0.016–0.06 | 0.03 | 0.03 |
| Penicillin-I | 0.016–0.125 | 0.03 | 0.03 |
| Penicillin-R | 0.016–0.06 | 0.03 | 0.03 |

[a] Penicillin-S, penicillin susceptible; Penicillin-I, penicillin intermediate; Penicillin-R, penicillin resistant.

also dispensed alone in the first column. Inocula were prepared by suspending growth from the blood agar plates in sterile saline to a density equivalent to that of a 0.5 McFarland standard and were diluted 1:10 to produce final inocula of $5 \times 10^5$ CFU/ml with a multipoint inoculator. Trays were incubated aerobically overnight. Standard quality control strains, including *S. pneumoniae* ATCC 49619 (16), were included with each run. Fractional inhibitory concentrations (FICs) were calculated as the MIC of drug A or B in the combination/the MIC of drug A or B alone, and the FIC index was obtained by adding the FICs. FIC indices were interpreted as synergistic if the values were ≤0.5, indifferent or additive if the values were >0.5 to 4.0, and antagonistic if the values were >4.0 (4).

**Time-kill determinations.** Three penicillin-susceptible, three penicillin-intermediate, and three penicillin-resistant strains were tested as described previously (18). Both β-lactams and glycopeptides were tested alone and in combination. In each case, concentrations four times above and four times below the MICs were tested. Viability counts were determined at 0, 6, 12, and 24 h. Drug carryover was addressed as described previously (18). Synergy was defined as a ≥2 $\log_{10}$ decrease in the viable count with the combination at 24 h compared with that of the more active of each of the two compounds tested alone (8).

**Statistical determination.** Statistical determination was performed by the McNemar test for significance of changes with William's correction.

## RESULTS

The penicillin MICs at which 50 and 90% of isolates are inhibited ($MIC_{50}$s and $MIC_{90}$s), respectively for susceptible, intermediate, and resistant strains were 0.016 and 0.06, 0.25 and 1.0, and 2.0 and 4.0 μg/ml, respectively. The MICs of the individual drugs for the pneumococcal strains tested are presented in Table 1. Cefpirome MICs were usually 1 dilution lower than those of cefotaxime for all groups, especially for penicillin-resistant strains, with all strains being inhibited by ≤1.0 μg/ml. Teicoplanin MICs were lower than those of vancomycin, with $MIC_{90}$s of 0.03 μg/ml for the former compared with $MIC_{90}$s of 0.25 μg/ml for the latter. The results of the checkerboard titration tests are presented in Table 2. Synergy between cefotaxime and vancomycin, was found for 51 strains, synergy between cefpirome and vancomycin was found for 31 strains, synergy between cefotaxime and teicoplanin was found for 27 strains, and synergy between cefpirome and teicoplanin was found for 18 strains. Synergy was seen for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant strains. However, for penicillin-resistant strains synergy between cefotaxime and vancomycin was significantly ($P < 0.005$) more common than that between cefpirome and vancomycin. For only three strains were FIC indices 2.0 (an FIC index of >1.0 to 4.0 indicates indifference): between cefpirome and vancomycin for two strains and between cefotaxime and vancomycin for one strain. All other FIC indices in the additive or indifferent range were between >0.5 and 1.0, and no antagonistic FIC indices (>4.0) were observed.

The results of time-kill testing compared with those obtained by the checkerboard titration method are presented in Table 3, and time-kill curves for two strains are presented in Fig. 1 and 2. Synergy was found for all four drug combinations by time-kill techniques for all nine strains (including strain 42, for which FIC indices were 2.0 with cefpirome-vancomycin and cefotaxime-vancomycin).

## DISCUSSION

The results of the present study confirm the superior in vitro activity of cefpirome compared with that of cefotaxime, especially against penicillin-resistant pneumococci (2, 5, 8, 21). Even for pneumococci for which penicillin MICs are in the range of 2.0 to 8.0 μg/ml, indicating resistance, the highest cefpirome MIC was 1.0 μg/ml, which is 1 dilution below the corresponding value for cefotaxime. No breakpoints for cefpirome exist for pneumococci; however, by using the cefotaxime resistance breakpoint of ≥2.0 μg/ml (17), all pneumococci would be susceptible or intermediate to cefpirome in the present study. Although this difference may be small, it may critically affect the therapeutic response in patients with meningitis, in whom cerebrospinal fluid cephalosporin concentrations are close to the MICs for resistant strains (8). The superior activity of teicoplanin compared with that of vancomycin has also been described before (9).

Using a pharmacodynamic model simulating the concentration profile in cerebrospinal fluid, Fitoussi and colleagues (5) have demonstrated the bactericidal activity of cefpirome alone at 6 h (mean killing, 3.51 ± 0.34 $\log_{10}$ CFU/ml) against all pneumococcal strains for which cefpirome MICs were <0.5 μg/ml. By contrast, against strains for which cefpirome MICs were ≥0.5 μg/ml, killing was significantly lower, with a mean reduction of 2.86 ± 0.57 $\log_{10}$ CFU/ml. In another model of pneumococcal meningitis, Friedland et al. (8) found cefpirome to be bactericidal, with a killing activity of 3.3 $\log_{10}$ CFU/ml within 5 h against a pneumococcal strain for which the cefpirome MIC was 0.5 μg/ml.

Klugman and Capper (12) have reported synergy between cefpirome at its MIC combined with vancomycin at half its

TABLE 2. Strains for which FIC indices in checkerboard titrations indicated drug synergism

| Penicillin resistance category (no. of strains) | No. of strains | | | |
|---|---|---|---|---|
| | Cefpirome-vancomycin | Cefpirome-teicoplanin | Cefotaxime-vancomycin | Cefotaxime-teicoplanin |
| Susceptible (35) | 19 | 5 | 16 | 6 |
| Intermediate (34) | 10 | 6 | 18 | 10 |
| Resistant (31) | 2[a] | 7 | 17[a] | 11 |
| All strains (100) | 31 | 18 | 51 | 27 |

[a] $P < 0.005$.

TABLE 3. Comparison of results by checkerboard and time-kill studies

| Strain[a] | Result for the following drug combinations by the indicated method[a]: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cefpirome-teicoplanin | | Cefpirome-vancomycin | | Cefotaxime-teicoplanin | | Cefotaxime-vancomycin | |
| | C[b] | T[b] | C | T | C | T | C | T |
| 153 (Su) | I | Sy | I | Sy | I | Sy | I | Sy |
| 60 (Su) | I | Sy | Sy | Sy | I | Sy | Sy | Sy |
| 149 (Su) | I | Sy | I | Sy | I | Sy | Sy | Sy |
| 5 (In) | I | Sy | Sy | Sy | I | Sy | Sy | Sy |
| 42 (In) | I | Sy | I | Sy | I | Sy | I | Sy |
| 42B (In) | Sy | Sy | Sy | Sy | Sy | Sy | Sy | Sy |
| 24 (R) | I | Sy | I | Sy | I | Sy | Sy | Sy |
| 227 (R) | I | Sy | I | Sy | I | Sy | Sy | Sy |
| 167 (R) | I | Sy | I | Sy | Sy | Sy | I | Sy |

[a] Su, penicillin susceptible; In, penicillin intermediate; R, penicillin resistant.
[b] C, checkerboard titration method; T, time-kill method; Sy, synergistic; I, indifferent or additive.

MIC against three penicillin-susceptible, three intermediate, and three resistant pneumococci, with a mean reduction at 6 h for organisms treated with the combination compared with those treated with the single agent of 4.73, 4.42, and 6.53 logs, respectively. In another study, Friedland and coworkers (8) described drug synergy (defined as a $\geq$2-$\log_{10}$ decrease in the numbers of CFU per milliliter between the combination of ceftriaxone and vancomycin and the most active single agent) against one penicillin-intermediate and one penicillin-resistant pneumococcal strain (8). Additionally, Klugman and coworkers (13) reported that the cerebrospinal fluid of patients treated with ceftriaxone plus vancomycin yielded greater bactericidal activity against two broad-spectrum cephalosporin-resistant pneumococcal strains than the cerebrospinal fluid of patients treated with ceftriaxone alone (13).

The results of the current study indicate that combinations of cefpirome or cefotaxime with teicoplanin or vancomycin yield FIC indices indicating either synergism or additivity-indifference, with none of the combinations being antagonistic. Time-kill studies confirmed the synergistic effects of these combinations. However, the sensitivities of the two methods differed. For one penicillin-intermediate strain (strain 42) FIC indices between both cefotaxime and cefpirome and vancomycin were 2.0, borderline synergy was found by the time-kill method for cefotaxime and vancomycin (2-log decrease) but clear synergy was found between cefpirome and vancomycin ($\geq$4-log decrease) at one-half to one-eighth the MIC. It may be that the time-kill methodology is more sensitive than checkerboard titration in detecting synergy between β-lactams and glycopeptides against pneumococci.

Initial empiric therapy for bacterial meningitis should be based on the possibility that penicillin-intermediate or penicillin-resistant pneumococci could be responsible for the patient's illness. Under these circumstances, therapy with ceftriaxone or cefotaxime combined with vancomycin is recommended (19). Vancomycin should not routinely be used alone owing to its unpredictable penetration into the cerebrospinal fluid (24). The results of synergy studies in our and other laboratories support the clinical recommendation given above. Little has been published on experimental models of cefpirome for the treatment of pneumococcal meningitis. Friedland et al. (8) have reported increased bacterial killing by cefpirome compared with that by ceftriaxone in rabbits infected with a penicillin-resistant pneumococcus. Täuber and colleagues (23)

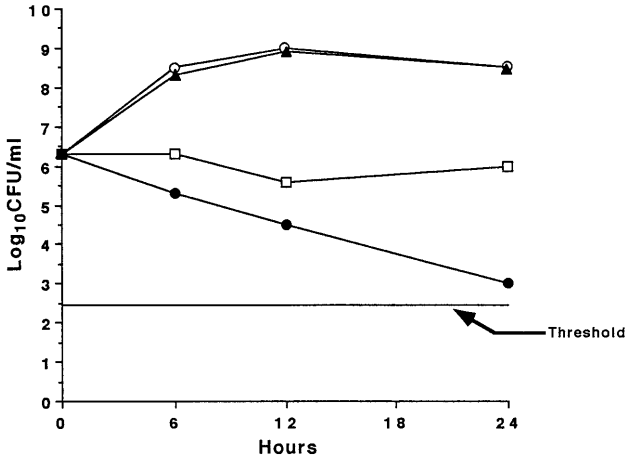


FIG. 1. Time-kill synergy study results for strain 42. The MICs of the individual agents were as follows: cefpirome, 0.06 μg/ml; cefotaxime, 0.125 μg/ml; vancomycin, 0.5 μg/ml; teicoplanin, 0.125 μg/ml. ○, growth control; □, cefotaxime at 0.06 μg/ml; ▲, teicoplanin at 0.06 μg/ml; ●, cefotaxime at 0.06 μg/ml and teicoplanin at 0.06 μg/ml.

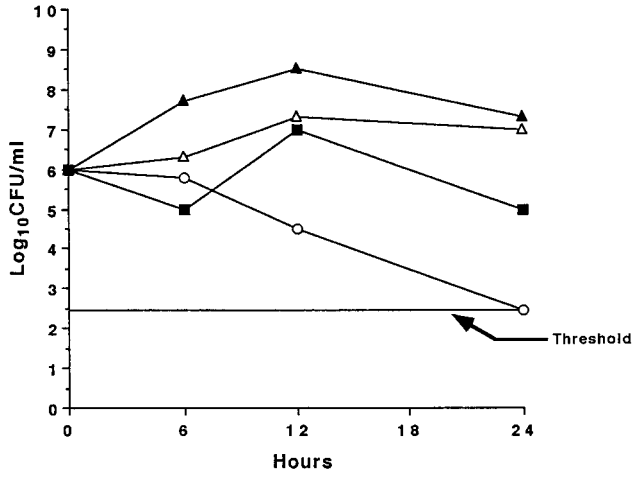


FIG. 2. Time-kill synergy study results for strain 42B. The MICs of the individual agents were as follows: cefpirome, 0.125 μg/ml; cefotaxime, 0.25 μg/ml; vancomycin, 0.5 μg/ml; teicoplanin, 0.125 μg/ml. ▲, growth control; ■, cefotaxime at 0.125 μg/ml; △, teicoplanin at 0.06 μg/ml; ○, cefotaxime at 0.125 μg/ml and teicoplanin at 0.06 μg/ml.

demonstrated good penetration of cefpirome into the cerebrospinal fluid of infected rabbits (21.8% ± 6.4% of the levels in serum); cefpirome also achieved maximal bactericidal rates at lower concentrations in cerebrospinal fluid (relative to the MBC) than those of the other broad-spectrum cephalosporins tested (including cefotaxime). We could not find any clinical reports of the use of cefpirome for the treatment of human meningitis caused by penicillin-intermediate and penicillin-resistant pneumococci. In the case of teicoplanin, more work on the pharmacokinetics and the penetration of this agent past the blood-brain barrier needs to be done before any recommendations can be made on the role of this compound for the treatment of pneumococcal meningitis.

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