Activities of Oral and Parenteral Agents against Penicillin-Susceptible and -Resistant Pneumococci

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This study examined bacteriostatic and bactericidal activities of oral and parenteral antibiotics for penicillin-susceptible and immediately and fully penicillin-resistant pneumococci. β-Lactamase inhibitors did not affect β-lactam results. The activities of ampicillin, amoxicillin ± clavulanate, WY-49605, cefuroxime, cefpodoxime, cefdinir, cefixime, and cefaclor against two penicillin-susceptible, two immediately penicillin-resistant, and two fully penicillin-resistant pneumococcal strains were tested. For all three groups, bacteriostatic values of amoxicillin and WY-49605 were lower than were those of other β-lactams tested. Of the cephalosporins, cefdinir, cefuroxime, and cefpodoxime yielded the lowest bacteriostatic values. All β-lactams were bactericidal (reduced original counts by ≥3 log10 CFU/ml) at 1 dilution above bacteriostatic values, except for cefpodoxime (bactericidal at 2 dilutions above bacteriostatic values for one susceptible strain and one immediately resistant strain), cefuroxime (bactericidal at 2 dilutions above bacteriostatic values for one immediately resistant strain), and ampicillin (bactericidal at 2 dilutions above bacteriostatic values for one immediately resistant strain). The activities of piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanate, ampicillin, amoxicillin-sulbactam, ceftriaxone, ceftazidime, and ciprofloxacin against four penicillin-susceptible, two immediately penicillin-resistant, and four fully penicillin-resistant pneumococcal strains were evaluated. Bacteriostatic values of piperacillin, ampicillin, and ceftriaxone for all groups were lower than were those of ticarcillin and ceftazidime. Bacteriostatic values of ciprofloxacin were unaffected by penicillin susceptibility. All β-lactams were bactericidal at 1 dilution above the bacteriostatic value, except for piperacillin (bactericidal at 2 dilutions above the bacteriostatic value for one immediately resistant strain), ticarcillin (bactericidal at 2 dilutions above the bacteriostatic value for one susceptible strain and one resistant strain), ampicillin (bactericidal at 2 dilutions above the bacteriostatic value for two resistant strains), ceftriaxone (bactericidal at 2 dilutions above the bacteriostatic value for one resistant strain), and ceftazidime (bactericidal at 2 dilutions above the bacteriostatic value for one susceptible strain).

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 2 decades and in particular the past 5 years (1). The main foci of penicillin-resistant pneumococci are currently South Africa, Spain, and Eastern Europe. However, wherever susceptibility testing is performed by appropriate methods, resistant strains are almost universally found (1). The spread of penicillin-resistant clones from country to country and from continent to continent demonstrates the capability of these strains to spread rapidly throughout the world (16, 17). In the United States, recent surveys (4, 29) have shown an increase in 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 (with 1.3% of isolates requiring MICs of ≥2.0 μg/ml). The problem has recently been exacerbated by the appearance of pneumococci with high-level resistance to cefotaxime and ceftazidime (3, 6, 23).

Although nonmeningeal infections caused by immediately and fully penicillin-resistant pneumococci may be treated parenterally under certain conditions with high doses of penicillin and other β-lactams, treatment may not always be successful. By contrast, clinical failure of penicillin in treatment of meningitis caused by strains immediately resistant to penicillin approaches 80%, and very few cases of meningitis caused by strains fully resistant to penicillin have responded to penicillin therapy (8, 9, 31). There is currently no standardized oral therapy for otitis media caused by immediately and fully penicillin-resistant pneumococci (8, 9).

The distribution of resistant strains is highly variable in the United States. Block and coworkers (2) have recently reported a 28% incidence rate of penicillin-resistant pneumococci from middle ear fluid of children with acute otitis media in Kentucky and a 29% incidence level of these strains in nasopharyngeal cultures from children with otitis media in Tennessee.

There is an urgent need for oral and parenteral β-lactams which can be used for infections such as meningitis, bacteremia, pneumonia, bronchitis, sinusitis, and otitis media caused by immediately and fully penicillin-resistant pneumococci. Previous studies have documented relatively high MICs of all groups of oral cephalosporins for these strains, with cefdinir, cefuroxime, and cefpodoxime yielding the lowest MICs for the group (7, 15, 19, 22, 27, 28, 30). Amoxicillin has MICs lower than those of penicillin G, ampicillin, and oral cephalosporins for these strains (7, 22, 27). WY-49605, a new broad-spectrum penem, has MICs 1 or 2 dilutions lower than those of amoxicillin for penicillin-susceptible and -resistant pneumococci (27). Previous studies have confirmed the low MICs of piperacillin compared with those of ticarcillin and ceftazidime for penicillin-susceptible and immediately and fully penicillin-resistant pneumococci (21, 31, 32).

The present study confirms and extends the above-described findings, by examining the bacteriostatic and bactericidal ac-

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Table 1. Bacteriostatic and bactericidal levels of oral agents for pneumococcal strains

<table>
<thead>
<tr>
<th>Strain&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Amoxicillin-clavulanate</th>
<th>Cefixime</th>
<th>Cefpodoxime</th>
<th>Cefdinir</th>
<th>Cefaclor</th>
<th>Cefuroxime</th>
<th>WY-49605</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (S)</td>
<td>0.008/0.008</td>
<td>0.016/0.016</td>
<td>0.010/0.016</td>
<td>0.064/0.125</td>
<td>0.016/0.064</td>
<td>0.064/0.064</td>
<td>2/2</td>
<td>0.016/0.032</td>
<td>0.016/0.016</td>
</tr>
<tr>
<td>294 (S)</td>
<td>0.008/0.008</td>
<td>0.016/0.016</td>
<td>0.010/0.016</td>
<td>0.25/0.5</td>
<td>0.032/0.064</td>
<td>0.064/0.064</td>
<td>5/0.5</td>
<td>0.064/0.064</td>
<td>0.008/0.016</td>
</tr>
<tr>
<td>5 (I)</td>
<td>0.5/0.5</td>
<td>0.064/0.064</td>
<td>0.064/0.064</td>
<td>4.0/4.0</td>
<td>0.25/1.0</td>
<td>0.25/0.25</td>
<td>2/2</td>
<td>1.0/1.0</td>
<td>0.125/0.125</td>
</tr>
<tr>
<td>42 (I)</td>
<td>0.064/0.25</td>
<td>0.032/0.032</td>
<td>0.032/0.032</td>
<td>2/2</td>
<td>0.064/0.125</td>
<td>0.064/0.125</td>
<td>1/0.2</td>
<td>0.125/0.5</td>
<td>0.064/0.125</td>
</tr>
<tr>
<td>167 (R)</td>
<td>2/0.4</td>
<td>4/8</td>
<td>4/8</td>
<td>6/8</td>
<td>128/128</td>
<td>128/128</td>
<td>2/8</td>
<td>1/0.2</td>
<td>0.125/0.5</td>
</tr>
<tr>
<td>33 (R)</td>
<td>4/0.8</td>
<td>8/0.8</td>
<td>8/0.8</td>
<td>8/0.8</td>
<td>8/0.8</td>
<td>8/0.8</td>
<td>8/0.8</td>
<td>1/0.2</td>
<td>0.125/0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> S. penicillin susceptible; I. = intermediately penicillin resistant; R. penicillin resistant.

Table 2. Bacteriostatic and bactericidal levels of parenteral β-lactams and ciprofloxacin for pneumococcal strains

<table>
<thead>
<tr>
<th>Strain&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Penicillin</th>
<th>Piperacillin</th>
<th>Ceftriaxone</th>
<th>Cefazidime</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (S)</td>
<td>0.008/0.008</td>
<td>0.016/0.016</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>61 (S)</td>
<td>0.008/0.016</td>
<td>0.016/0.016</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>153 (S)</td>
<td>0.032/0.064</td>
<td>0.016/0.016</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>294 (S)</td>
<td>0.016/0.016</td>
<td>0.032/0.032</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>42 (I)</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>5 (I)</td>
<td>0.25/0.25</td>
<td>0.5/0.5</td>
<td>0.5/0.5</td>
<td>0.5/0.5</td>
<td>WY-49605</td>
</tr>
<tr>
<td>167 (R)</td>
<td>1/1</td>
<td>1/1</td>
<td>0.125/0.25</td>
<td>0.125/0.25</td>
<td>WY-49605</td>
</tr>
<tr>
<td>33 (R)</td>
<td>4/8</td>
<td>4/8</td>
<td>4/8</td>
<td>1/0.2</td>
<td>WY-49605</td>
</tr>
<tr>
<td>228 (R)</td>
<td>2/2</td>
<td>4/8</td>
<td>4/8</td>
<td>32/64</td>
<td>WY-49605</td>
</tr>
<tr>
<td>38 (R)</td>
<td>4/4</td>
<td>4/4</td>
<td>4/4</td>
<td>32/64</td>
<td>WY-49605</td>
</tr>
</tbody>
</table>

<sup>a</sup> S. penicillin susceptible; I. = intermediately penicillin resistant; R. penicillin resistant.
Table 1, bacteriostatic values for penicillin-susceptible and intermediately and fully penicillin-resistant pneumococci were all lower for amoxicillin and WY-49605 than for other oral β-lactams tested. Amoxicillin bacteriostatic levels were 1 to 3 dilutions lower than those of penicillin G and ampicillin in intermediately resistant and resistant strains. Cefdinir, cefuroxime, and cefpodoxime yielded the lowest cephalosporin bacteriostatic levels, with cefaclor and cefixime yielding higher values. Levels of cefdinir, cefuroxime, and cefpodoxime were ≥1 dilution higher than those of amoxicillin for most strains.

Examples of results for one intermediately penicillin-resistant organism (strain 5) are presented in Fig. 1, and bacteriostatic values of oral agents for all strains are presented in Table 1. Bacteriostatic and bactericidal values were generally identical for the two penicillin-susceptible strains and tended to differ by 1 dilution for three of the four intermediately resistant and resistant strains. All oral β-lactams were bactericidal at 1 dilution above the MIC, except for cefpodoxime (bactericidal at 2 dilutions above the bacteriostatic level for one penicillin-susceptible strain and one intermediately penicillin-resistant strain), cefuroxime (bactericidal at 2 dilutions above the bacteriostatic level for one intermediately penicillin-resistant strain), and ampicillin (bactericidal at 2 dilutions above the bacteriostatic level for one intermediately penicillin-resistant strain).

As can be seen from Table 2, bacteriostatic values of parenteral agents for all pneumococcal groups were lower for piperacillin (susceptible, 0.016 to 0.032 μg/ml; intermediately resistant, 0.125 to 1.0 μg/ml; resistant, 4.0 μg/ml), ampicillin (susceptible, 0.016 to 0.032 μg/ml; intermediately resistant, 0.064 to 0.125 μg/ml; resistant, 1.0 to 2.0 μg/ml), and ceftriaxone (susceptible, 0.008 to 0.016 μg/ml; intermediately resistant, 0.064 μg/ml; resistant, 0.5 to 2.0 μg/ml) than for ticarcillin (susceptible, 0.5 to 1.0 μg/ml; intermediately resistant, 8.0 to 32.0 μg/ml; resistant, 64.0 to 128.0 μg/ml) and ceftazidime (susceptible, 0.064 to 0.125 μg/ml; intermediately resistant, 1.0 to 2.0 μg/ml; resistant, 8.0 to 32.0 μg/ml). Bacteriostatic values for ciprofloxacin (0.5 to 2.0 μg/ml) were unaffected by penicillin susceptibility.

All parenteral β-lactams were bactericidal (reduced colony counts by $\geq 3$ log$_{10}$ CFU/ml) at 1 dilution above the bacteriostatic value, except for piperacillin (bactericidal at 2 dilutions above the bacteriostatic level for one intermediately resistant strain), ticarcillin (bactericidal at 2 dilutions above the bacteriostatic level for one susceptible strain and one resistant strain), ampicillin (bactericidal at 2 dilutions above the bacteriostatic level for two resistant strains), ceftriaxone (bactericidal at 2 dilutions above the bacteriostatic level for one resistant strain), and ceftazidime (bactericidal at 2 dilutions above the bacteriostatic level for one susceptible strain).

**DISCUSSION**

Studies of bacteriostatic and bactericidal levels are useful methods to examine the kinetic interaction between bacteria and antimicrobial agents. The viable-count threshold of a method, taking amoxicillin or amoxicillin-clavulanate than from those taking cefixime ($P < 0.0001$), erythromycin-sulfisoxazole ($P = 0.0001$), or cefaclor ($P = 0.029$). Gehanno and coworkers (10) have found clinical success rates of 93% (39 of 42 cases), 91% (10 of 11 cases), and 75% (24 of 32 cases) with oral cefuroxime axetil treatment of otitis media associated with penicillin-resistant pneumococci, respectively. However, numbers in the intermediately resistant category were small. No other studies with any other oral cephalosporins against otitis media caused by penicillin-resistant pneumococci are currently available.

Lower MICs of piperacillin for penicillin-susceptible, intermediately penicillin-resistant, and penicillin-resistant pneumococci compared with those of ticarcillin ± clavulanate and ceftazidime have been reported before, both by us (21) and by
FIG. 1. Time-kill kinetics of different drugs against an intermediately penicillin-resistant pneumococcal strain (strain 5) at 0, 6, 12, and 24 h.
other workers (31, 32). High MICs of ceftazidime, in contrast to lower MICs of ceftriaxone for intermediately and fully resistant pneumococcal strains, have also previously been described (15, 26, 31). MICs of ampicillin are similar to those reported previously (7, 22). The present study confirms and extends the above-described findings.

Most penicillin-resistant pneumococci isolated in the United States are of the intermediately resistant variety (1, 8, 9). In view of the pharmacokinetic findings of Sörgel and Kinzig (25), serum piperacillin levels well above the agar dilution MIC and bacteriostatic and bactericidal levels can certainly be achieved for intermediately penicillin-resistant and possibly also penicillin-resistant pneumococci. Although in vitro results for ampicillin were similar to those for piperacillin, pharmacokinetics of piperacillin are more favorable, pointing to higher levels in serum than those of ampicillin (13, 25).

Data for ceftriaxone obtained in this study further support use of this compound for systemic infections (including meningitis) caused by intermediately penicillin-resistant pneumococci (15, 26, 31). However, with a resistance breakpoint of ≥2.0 µg/ml (18), the bacteriostatic and bactericidal values for two of four penicillin-resistant strains, and the bactericidal value for a third resistant strain, were in the ceftriaxone-resistant category.

Data for ciprofloxacin indicate that bacteriostatic and bactericidal levels cluster around the susceptibility breakpoint: this and other currently available quinolones such as ofloxacin should not be used as first-line treatment of systemic pneumococcal infections caused by penicillin-susceptible or -resistant strains (8, 9, 28).

There are currently no breakpoints for pneumococci recommended by the National Committee for Clinical Laboratory Standards for the parenteral β-lactams tested in this study other than ceftriaxone (18). In view of the rapid worldwide spread of penicillin-resistant strains, development of breakpoints for these agents is clearly needed. Bacteriostatic and bactericidal levels of piperacillin for resistant pneumococci are lower than reported levels in serum and tissue (25): this is particularly true for intermediately resistant strains, which compose >90% of penicillin-resistant pneumococci isolated in the United States (1, 4). Additionally, in view of favorable pharmacokinetic data, serum piperacillin levels sufficient to inhibit intermediately and possibly fully resistant organisms may be achievable in humans.

It is important to note that for most antibiotics tested, activity against penicillin-resistant strains was clearly lower than activity against intermediately penicillin-resistant pneumococci. Therefore, possible use of such agents for treatment of infections caused by pneumococci for which MICs are ≥2.0 µg/ml cannot be recommended at this time.

In summary, on the basis of MICs and studies of bacteriostatic and bactericidal levels, including results presented in this paper, all oral compounds tested are potentially of use in conditions such as otitis media in areas where intermediately penicillin-resistant pneumococci are uncommon. However, in areas where these strains are frequently found, amoxicillin ± clavulanate may be a logical choice, based on favorable susceptibility kinetics, the lowest MICs of all currently available oral β-lactams for penicillin-susceptible and intermediately penicillin-resistant pneumococci, and activity against Haemophilus influenzae and Moraxella catarrhalis. Cefuroxime and cefpodoxime may also be of use, although their bacteriostatic levels are higher than those of amoxicillin. WY-49605 is of potential interest but requires human pharmacokinetic and clinical studies. Cefuroxime, cefpodoxime, and WY-49605 are also active against H. influenzae and M. catarrhalis. Piperacillin ± tazobactam may represent an alternative to cefotaxime or ceftriaxone for therapy of systemic nosocomial infections caused by these strains. Clinical studies will be necessary to prove the above hypotheses and also to delineate the role of these compounds in treatment of infections caused by penicillin-resistant pneumococci.

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