In Vitro Comparison of N-Formimidoyl Thienamycin (MK0787) and Azlocillin with Three Aminoglycosides and Ticarcillin Against Pseudomonas aeruginosa

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The activities of N-formimidoyl thienamycin and azlocillin were compared with those of tobramycin, gentamicin, amikacin, and ticarcillin against 175 Pseudomonas aeruginosa isolates, including 24 strains with known mechanisms of resistance to aminoglycosides. The 50% mean inhibitory concentration for azlocillin was lower than for ticarcillin, but the 90% mean inhibitory concentration was similar for both drugs. All susceptible and multidrug-resistant strains were susceptible to N-formimidoyl thienamycin.

Serious infections caused by Pseudomonas aeruginosa are associated with a high mortality rate, especially in patients with serious underlying disease, (1, 2, 6). N-Formimidoyl thienamycin (MK0787), a more stable β-lactam antibiotic than the parent compound, and azlocillin, a new ureido penicillin, have been shown to possess potent activity against many microbial strains, including P. aeruginosa (3–5, 7–13, 15, 17, 18).

The susceptibility of 220 strains (including 109 blood culture isolates) from two large Albany area hospitals was tested for N-formimidoyl thienamycin and azlocillin. The susceptibility of 151 of these isolates was also tested for gentamicin, tobramycin, amikacin, and ticarcillin. In addition, 24 isolates with known mechanisms of resistance to selected aminoglycosides (permeability mutation or enzyme inactivation) were obtained from Bristol Laboratories (courtesy of P. Kresel). N-Formimidoyl thienamycin, azlocillin, tobramycin, gentamicin, amikacin, and ticarcillin were obtained from Merck Sharp & Dohme, Delbay Research Corp., Eli Lilly & Co., Schering Corp., Bristol Laboratories, and Beecham Laboratories, respectively. All antibiotic solutions were used on the day of preparation. Antibiotic susceptibilities were determined by using the agar-dilution technique as described by Washington and Sutter (16), using the replica of Steers et al. (14).

The 50% mean inhibitory concentration (MIC50) and MIC90 for 220 strains of P. aeruginosa for N-formimidoyl thienamycin were 2 and 8 μg/ml (geometric mean MIC [GmMIC] 2.8 μg/ml) and for azlocillin were 16 and 128 μg/ml (GmMIC 26 μg/ml), respectively. The activity of N-formimidoyl thienamycin and azlocillin was compared with reference antibiotics against 151 isolates of P. aeruginosa. The MIC50, MIC90, range, and GmMIC in micrograms per milliliter were as follows: N-formimidoyl thienamycin, 2, 4, 0.5 to 32, and 2.5; azlocillin, 16, 128, 4 to 1,024, and 26.5; tobramycin, 1, 4, 0.125 to >64, and 1.7; gentamicin, 4, 16, 0.125 to >512, and 517; amikacin, 8, 32, 0.5 to 64, and 7.7; and ticarcillin, 32, 128, 8 to >1,024, and 39.8. Table 1 shows the activity of N-formimidoyl thienamycin against strains resistant to one or more reference antibiotics. We found that 4 μg/ml of N-formimidoyl thienamycin inhibited >86% of the P. aeruginosa strains tested and that 32 μg/ml inhibited all of the P. aeruginosa strains tested. The activity of N-formimidoyl thienamycin against seven strains intermediate or highly resistant to azlocillin and reference antibiotics showed that five strains were inhibited by <4 μg/ml and all strains were inhibited by 32 μg of N-formimidoyl thienamycin per ml. For 24 strains of P. aeruginosa with known mechanisms of resistance for amikacin, tobramycin, or both, all but one strain was inhibited by <8 μg/ml of N-formimidoyl thienamycin (Table 2). Of these 24 strains resistant to azlocillin (MIC ≥64 μg/ml) 14 were susceptible to ≤8 μg/ml of N-formimidoyl thienamycin.

Our data compare closely with published studies which included smaller numbers of P. aeruginosa strains (4, 8, 9, 11, 12, 15). Of special interest in the present study was the activity of N-formimidoyl thienamycin against strains of P. aeruginosa resistant to one, more than one, or
all of the reference antibiotics used in this study. Regardless of resistance to one or more of the antibiotics used (azlocillin, ticarcillin, tobramycin, gentamicin, and amikacin), the GmMIC for N-formimidoyl thienamycin remained low, i.e., 2.6 to 4 μg/ml. Of the seven strains with intermediate or marked resistance to all of the reference antibiotics, five had an MIC <4 μg/ml for N-formimidoyl thienamycin. Furthermore, the mechanism of resistance to selected aminoglycosides did not influence the susceptibility of the P. aeruginosa strains to N-formimidoyl thienamycin. As noted by Livingston et al., however, and as shown in our study, the highly resistant strains to aminoglycosides have only a slightly higher MIC for N-formimidoyl thienamycin (12). This study also indicates that azlocillin has greater activity than does ticarcillin against the P. aeruginosa strains tested (GmMIC, 26.5 and 39.8 μg/ml, respectively). However, the MIC90 is similar with both drugs, i.e., 128 μg/ml. Similar findings were observed previously by Fu and Neu (7). Strains shown to be resistant to azlocillin (MIC, >64 μg/ml) were susceptible to ≤8 μg/ml of N-formimidoyl thienamycin (GmMIC, 3.2 μg/ml).

The activity of N-formimidoyl thienamycin against P. aeruginosa, including multiresistant strains to the presently available antibiotics, is excellent. These findings and the evidence for increased activity of azlocillin over ticarcillin suggest the possibility of better agents for the future therapy of P. aeruginosa infections.

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LITERATURE CITED


TABLE 1. N-Formimidoyl thienamycin activity against P. aeruginosa strains resistant to one or more aminoglycosides or penicillins

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. of isolates</th>
<th>MIC (μg/ml)</th>
<th>Range</th>
<th>GmMIC</th>
<th>MIC50</th>
<th>MIC90</th>
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<tbody>
<tr>
<td>Tobramycin (MIC ≫ 8)</td>
<td>15</td>
<td>1–32</td>
<td>3.5</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gentamicin (MIC ≫ 8)</td>
<td>65</td>
<td>0.5–32</td>
<td>2.6</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Amikacin (MIC ≫ 32)</td>
<td>26</td>
<td>1–32</td>
<td>3.1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Azlocillin (MIC ≫ 128)</td>
<td>28</td>
<td>1–8</td>
<td>3.2</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ticarcillin (MIC ≫ 128)</td>
<td>29</td>
<td>0.5–32</td>
<td>2.7</td>
<td>2</td>
<td>8</td>
<td></td>
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</tbody>
</table>

TABLE 2. N-Formimidoyl thienamycin activity against P. aeruginosa strains resistant to aminoglycosides because of decreased antibiotic uptake (amikacin) or inactivating enzymes (amikacin-tobramycin)

<table>
<thead>
<tr>
<th>Resistance mechanism</th>
<th>No. of strains</th>
<th>Antibiotic</th>
<th>MIC (μg/ml)</th>
<th>Range</th>
<th>GmMIC</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased uptake</td>
<td>13</td>
<td>Amikacin</td>
<td>1–16</td>
<td>4.0</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Enzymatica</td>
<td>11</td>
<td>Amikacin + tobramycin</td>
<td>2–8</td>
<td>3.3</td>
<td>2</td>
<td>4</td>
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