In Vitro Activity of New β-Lactam Antibiotics and Other Antimicrobial Drugs Against Anaerobic Isolates from Obstetric and Gynecological Infections

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Infections of the female genital tract are often of mixed aerobic/anaerobic bacterial etiology (2–4, 11). Thus, it is frequently necessary to use a combination of antibiotics to inhibit the variety of bacteria present, although treatment with a single antibiotic would be preferable. The fact that many of the new antibiotics are effective against a wider range of bacteria than most of the currently used antibiotics suggests that one or more of these may be useful in a single-agent regimen. However, although many in vitro studies have shown that these antibiotics inhibit the aerobic organisms common to obstetric and gynecological infections (1, 12–14), there are few and only limited studies (6, 7, 9) of the effectiveness of these antibiotics against species of anaerobic bacteria, such as Bacteroides bivius and anaerobic gram-positive cocci, commonly isolated from pelvic infections (3, 4; K. A. Rosene, G. P. Wager, L. Tompkins, H. Watkins, and D. A. Eschenbach. 21st Intersci. Conf. Antimicrob. Agents Chemother. abstr. no. 107, 1981).

In an effort to expand on the above experience, we determined the minimal inhibitory concentrations (MICs) of cefoperazone, cefotaxime, cefoxitin, chloramphenicol, clindamycin, N-formimidoyl thienamycin, metronidazole, moxalactam, penicillin G, and piperacillin for 158 anaerobic bacteria isolated from endometrial wash cultures of 56 women admitted to San Francisco General Hospital with untreated pelvic infections (mostly salpingitis and endometritis). The organisms, identified through the use of gas-liquid chromatography and prereduced anaerobically sterilized media (5), were either recent isolates maintained in chopped meat broth or subcultures of isolates frozen in 10% skim milk at −70°C. MICs were determined by the National Committee for Clinical Laboratory Standards agar dilution method on Wilkins-Chalgren agar (8) or, for organisms which would not grow on Wilkins-Chalgren agar, by the Wadsworth Medical Center agar dilution test on supplemented brucella blood agar (10). Standard reference powders of each antibiotic were provided by the manufacturers. Two of three control organisms (Bacteroides fragilis ATCC 25285, B. thetaiotaomicron ATCC 29741, or Peptococcus magnus ATCC 29328) were run with each batch of tests performed.

Tables 1 and 2 show the range of MICs of each antibiotic required for the organisms tested and the MICs at which at least 50% and 90% of the organisms were inhibited (MIC50 and MIC90).

N-formimidoyl thienamycin was the most active antibiotic, inhibiting 90% of the organisms at ≤0.125 μg/ml and all organisms at ≤0.5 μg/ml. Clindamycin was also active against the whole spectrum of organisms, with an MIC90 of 1.0 μg/ml or less. Although for most organisms the MICs of both clindamycin and metronidazole were similar, against B. bivius and the B. melaninogenicus group, clindamycin was markedly more active than metronidazole.

Although the activities of the penicillins and the cephalosporins varied, all appeared active against most of the organisms tested, except for the B. fragilis group. Moxalactam and cefoxitin were the most active of the cephalosporins and penicillins against the B. fragilis group, with moxalactam showing somewhat more activity than cefoxitin.
TABLE 1. Activities of new β-lactam antibiotics and other antimicrobial drugs against anaerobic cocci

<table>
<thead>
<tr>
<th>Organism (no. of isolates)</th>
<th>N-formimidoyl thienamycin</th>
<th>Chloramphenicol</th>
<th>Clindamycin</th>
<th>Metronidazole</th>
<th>Cefoperazone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC range</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>MIC range</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Peptococcus asaccharolyticus (31)</td>
<td>≤0.008–0.015</td>
<td>≤0.008</td>
<td>≤0.008</td>
<td>1–2</td>
<td>1</td>
</tr>
<tr>
<td>Peptococcus magnus (8)</td>
<td>≤0.008–0.03</td>
<td>0.015</td>
<td>0.03</td>
<td>1–4</td>
<td>2</td>
</tr>
<tr>
<td>Peptococcus prevotii (25)</td>
<td>≤0.008–0.03</td>
<td>≤0.008</td>
<td>0.015</td>
<td>0.5–2</td>
<td>1</td>
</tr>
<tr>
<td>Peptostreptococcus anaerobius (28)</td>
<td>≤0.008–0.5</td>
<td>0.015</td>
<td>0.125</td>
<td>0.25–2</td>
<td>1</td>
</tr>
<tr>
<td>Veillonella parvula (7)</td>
<td>0.015–0.125</td>
<td>0.03</td>
<td>0.03</td>
<td>0.25–2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<sup>a</sup> Concentrations are in micrograms per milliliter, except for penicillin G, which is given in units per milliliter.

<sup>b</sup> —, Not available. All MICs were ≤0.03 μg/ml.

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TABLE 1—Continued

<table>
<thead>
<tr>
<th>Cefotaxime</th>
<th>Cefoxitin</th>
<th>Moxalactam</th>
<th>Penicillin G</th>
<th>Piperacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC range</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>MIC range</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>≤0.03–0.5</td>
<td>0.06</td>
<td>0.25</td>
<td>≤0.03–1</td>
<td>≤0.03</td>
</tr>
<tr>
<td>0.25–2</td>
<td>0.5</td>
<td>1</td>
<td>≤0.03–0.125</td>
<td>0.06</td>
</tr>
<tr>
<td>≤0.03–0.25</td>
<td>0.06</td>
<td>0.25</td>
<td>≤0.03–0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>≤0.03–4</td>
<td>0.06</td>
<td>4</td>
<td>≤0.03–8</td>
<td>0.125</td>
</tr>
<tr>
<td>≤0.03–1</td>
<td>0.03</td>
<td>0.25</td>
<td>0.06–1</td>
<td>0.125</td>
</tr>
</tbody>
</table>
| MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % | MIC µg/ml | MIC % |MIC of the following antimicrobial agents:

**TABLE 2—Continued**

- Concentrations in micrograms per milliliter, except for those of penicillin G, which are in units per milliliter.
- s, spp., penicillinum, G: include S. m. aureus and G: / staphylococci.
- Bacteriostatic: Group includes: B. fragilis, B. melitis, and B. vulgaris.

- Concentrations are in concentrations of that organism, except for those of penicillin G, which are in units per milliliter.

- MIC of the following antimicrobial agents:
Against most isolates of the three Peptococcus spp. tested, the cephalosporins and penicillins were inhibitory at lower concentrations than was clindamycin.

A pattern of increased penicillin/cephalosporin concentrations needed for inhibition of some Peptostreptococcus anaerobius strains was noted. For 22 (79%) of the isolates, the MICs for cefoperazone and cefoxitin were \( \leq 1 \mu g/ml \); for penicillin G the MIC was \( \leq 0.06 \) U/ml; and for ceftaxime, moxalactam, and piperacillin, the MICs were \( \leq 0.25 \mu g/ml \). However, the MICs of these antibiotics were definitely increased for six (21%) of the isolates, with ranges of 1 to 16 \( \mu g/ml \) for cefoperazone, 4 to 8 \( \mu g/ml \) for cefotaxime and cefoxitin, 0.25 to 8 U/ml for penicillin G, 1 to 8 \( \mu g/ml \) for piperacillin, and 16 to 64 \( \mu g/ml \) for moxalactam. For \( N \)-formimidoyl thienamycin, the MICs for these same six isolates were also higher (0.06 to 0.5 \( \mu g/ml \)) than for the other 22 isolates (\( \leq 0.008 \) to 0.03 \( \mu g/ml \)). No increase in inhibitory concentrations of chloramphenicol, clindamycin, or metronidazole for any of the \( P. \) anaerobius isolates was evident.

The results of this study indicate that with the exception of \( N \)-formimidoyl thienamycin, the newer beta-lactam antibiotics which were tested have activities against anaerobes common to obstetric and gynecological infections similar to or less than that of cefoxitin, which is now frequently used to treat such infections. Thus, although they may provide effective treatment in many cases, they may be ineffective in others, especially those in which \( B. \) fragilis isolates are significant. Cefoperazone and cefotaxime, especially, showed poor activity against the \( B. \) fragilis group. Some isolates of \( P. \) anaerobius were resistant to moxalactam.

\( N \)-formimidoyl thienamycin, on the other hand, was highly active against all anaerobes tested. In general, it was more active than metronidazole and had activity similar to or greater than that of clindamycin against all organisms tested. Thus, \( N \)-formimidoyl thienamycin may provide a suitable alternative to clindamycin or metronidazole for treatment of anaerobic infections. Our data on the activity of \( N \)-formimidoyl thienamycin against anaerobes, coupled with other reports of its activity against aerobic organisms (1, 12–14), indicate that it might be a useful single agent in the treatment of polymicrobic pelvic infections and that carefully controlled clinical trials are warranted.

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LITERATURE CITED


