Comparative In Vitro Activities of Enoxacin (CI-919, AT-2266) and Eleven Antipseudomonal Agents Against Aminoglycoside-Susceptible and -Resistant Pseudomonas aeruginosa Strains

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The in vitro activity of enoxacin (CI 919, AT 2266), a new oral quinolone carboxylic acid compound, was compared with those of gentamicin, tobramycin, amikacin, azlocillin, piperacillin, aztreonam, moxalactam, imipenem, cefsulodin, ceftazidime, and cefoperazone against 101 aminoglycoside-susceptible and 105 aminoglycoside-resistant Pseudomonas aeruginosa strains. Among these 206 P. aeruginosa isolates were 25 strains with known mechanisms of resistance to amikacin. The activity of enoxacin was similar to that of tobramycin against aminoglycoside-susceptible strains, with MICs of 1.0 to 2.0 \( \mu \)g/ml and 0.5 to 1.0 \( \mu \)g/ml, respectively, for 90% of the strains. Enoxacin was the most active agent in this in vitro study against aminoglycoside-resistant P. aeruginosa strains, with MICs of 2.0 to 4.0 \( \mu \)g/ml for 90% of the strains. Strains with enzymatic resistance to amikacin were more resistant to \( \beta \)-lactams (except enoxacin and imipenem) than were strains with decreased permeability.

The broad antibacterial spectrum of enoxacin against gram-positive and gram-negative microorganisms, including Pseudomonas aeruginosa, has been shown by several investigators (3–5, 7, 10; S. A. Chartand, R. K. Scribner, M. I. Marks, and D. F. Welch, Cystic Fibrosis Club Abstracts, 22nd, San Francisco, 1981). In vivo studies with laboratory animals and human volunteers have shown that enoxacin is well absorbed by the oral route, slightly metabolized, and distributed to most tissues at concentrations higher than those found in plasma (6, 8, 9; R. Wolf, R. Eberi, A. Dunky, N. Mertz, T. Chang, J. R. Goulart, and J. Latts, J. Antimicrob. Chemother., in press). Wolf et al. reported that levels in plasma were linearly related to the dose administered and that renal clearance accounted for ca. 40% of the total body clearance of the drug. Peak drug concentrations of 4.3 \( \mu \)g/ml in serum followed the administration of 800 mg of enoxacin to human volunteers (Wolf et al., in press). Infections caused by P. aeruginosa in humans are difficult to treat, and therapy often includes parenteral administrations of antimicrobial agents (1, 2). Enoxacin may offer a therapeutic advantage as an antipseudomonal agent because of the low frequency of microbial resistance, its high tissue concentrations, and the oral route of administration. This study compares the activity of enoxacin with that of 11 other antimicrobial agents against 206 strains of P. aeruginosa.

We used the following antimicrobial agents: enoxacin (Warner-Lambert Co., Pharmaceutical Research Division, Ann Arbor, Mich.), azlocillin (Miles Laboratories, Inc., Elkhart, Ind.), amikacin (Bristol Laboratories, Syracuse, N.Y.), piperacillin (Lederle Laboratories, Pearl River, N.Y.), moxalactam and tobramycin (Eli Lilly & Co., Indianapolis, Ind.), aztreonam (E. R. Squibb & Sons, Inc., Princeton, N.J.), gentamicin (Schering Corp., Bloomfield, N.J.), cefoperazone (Roerig, New York, N.Y.), cefsulodin (Abbott Laboratories, North Chicago, Ill.), imipenem (Merck Sharp & Dohme, West Point, Pa.), and ceftazidime (Glaxo, Inc., Fort Lauderdale, Fla.). The antimicrobial agents were supplied as dry powders, with the exception of tobramycin, and stored at 4°C. All antibiotic solutions were prepared on the day of use.

A total of 206 clinical isolates of P. aeruginosa were tested against enoxacin, three aminoglycosides, and eight \( \beta \)-lactam antibiotics. All of the microorganisms with known susceptibility to aminoglycosides were obtained from two large hospitals in the Albany area. Of these 206 strains, 105 strains were resistant to one, two, or all three aminoglycosides (gentamicin and tobramycin MIC, \( \geq \)8 \( \mu \)g/ml; amikacin MIC, \( \geq \)32 \( \mu \)g/ml), and 101 isolates were susceptible (gentamicin and tobramycin MIC, \(< \)8 \( \mu \)g/ml; amikacin MIC, \(< \)32 \( \mu \)g/ml). Included in this study were 25 P. aeruginosa strains with known mechanisms of resistance to amikacin. Antibiotic susceptibilities were determined by the agar dilution technique as described by Washington and Sutter (12), by use of the replicator described by Steers et al. (11). Inocula were prepared from a 4- to 6-h broth culture of the organisms. The turbidity was initially adjusted to 10\(^7\) CFU/ml, and 1 \( \mu \)l of the final inoculum was applied to unsupplemented Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.). The MIC represents the lowest concentration at which complete inhibition occurred. A fine, barely visible haze or single colony was disregarded. The following ATCC strains were included as controls on each plate: Escherichia coli 25922 (enoxacin MIC, 0.125 \( \mu \)g/ml; P. aeruginosa 27853 (2.0 \( \mu \)g/ml), and Staphylococcus aureus 29213 (1.0 \( \mu \)g/ml).

Overall, the susceptibility to enoxacin was similar to that of 101 aminoglycoside-susceptible strains to tobramycin, with MIC\(_{90}\) of 1.0 to 2.0 and 0.5 to 1.0 \( \mu \)g/ml, respectively. Of the 10 remaining antibiotics, the MIC\(_{90}\) (in micrograms per milliliter) was 2.0 to 4.0 for gentamicin and imipenem, 4.0 for ceftazidime, 4.0 to 8.0 for amikacin, 8.0 to 16.0 for cefsulodin, 16.0 for aztreonam and piperacillin, 16.0 to 32.0 for cefoperazone, and 32.0 to 64.0 for azlocillin and moxalactam. For the amikacin-resistant P. aeruginosa strains, enoxacin had the lowest MIC\(_{90}\) (2.0 to 4.0 \( \mu \)g/ml). For the 11 reference antibiotics the MIC\(_{90}\) (in micrograms per milliliter) was 4.0 to 8.0 for imipenem, 8 to 16 for ceftazidime, 16...
TABLE 1. Enoxacin and β-lactam activities against amikacin-resistant P. aeruginosa strains

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Decreased uptake (n=12)</th>
<th>Enzymatic inhibition (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (μg/ml)</td>
<td>% 50</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4-16</td>
<td>8</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>4-16</td>
<td>4</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32-128</td>
<td>32</td>
</tr>
<tr>
<td>Cefsulodin</td>
<td>4-64</td>
<td>64</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>4-32</td>
<td>8</td>
</tr>
<tr>
<td>Azlocillin</td>
<td>4-64</td>
<td>64</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>2-64</td>
<td>8</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>4-64</td>
<td>16</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>8-64</td>
<td>16</td>
</tr>
</tbody>
</table>

*a Enoxacin and β-lactam antimicrobial susceptibility of 25 isolates with known mechanisms of resistance. The MIC90 and MIC50 were calculated from the distribution of MICs (cumulative percent inhibited) and were determined as the concentrations at which the number of isolates inhibited was closest to 50 and 90%, respectively. When two concentrations were equidistant from 50 or 90%, a range for the MIC was reported.

*b Inhibition caused by the following enzymes: aminoglycoside acetyltransferase (four strains), aminoglycoside phosphotransferase (two strains), aminoglycoside adenylytransferase (two strains), and aminoglycoside nucleotide transferase (five strains). Determination of mechanisms of resistance was performed by P. Kressel and D. Bobey, Bristol Laboratories, Syracuse, N.Y.

for cefsulodin, 32 for piperacillin, 32 to 64 for azlocillin, cefoperazone and moxalactam, 64 for aztreonam and amikacin, 128 for tobramycin, and 512 for gentamicin.

Table 1 shows the susceptibilities of 25 P. aeruginosa strains with known mechanisms of resistance to amikacin (12 strains with decreased uptake and 13 strains with enzymatic inhibition). Of these 25 strains, all but 1 was inhibited by ≥4.0 μg of enoxacin per ml. The MIC90s of azlocillin, imipenen, piperacillin, aztreonam, and moxalactam were similar, regardless of the mechanisms of resistance to amikacin. The MIC90s of enoxacin and ceftazidime and of cefsulodin and cefoperazone were one and two dilutions higher, respectively. However, whereas the upper value in the susceptibility range was only slightly higher for enoxacin, it was markedly higher for seven of the eight (imipenen excluded) β-lactams for strains with enzymatic inhibition than for strains with decreased drug uptake.

Our susceptibility data for enoxacin compare closely with those of previous studies which included smaller numbers of P. aeruginosa strains (3–5, 7; Chartrand et al., 1981). Compared with the reference drugs in this study, the MIC90 of enoxacin was lowest for aminoglycoside-resistant P. aeruginosa strains and similar to that of tobramycin for the aminoglycoside-susceptible strains. The mechanisms of resistance to amikacin had only a minimal effect on the susceptibility of P. aeruginosa strains to enoxacin. Because of its pharmacokinetic properties and low frequency of microbial resistance, enoxacin may offer a therapeutic advantage in the treatment of P. aeruginosa infections, including those caused by aminoglycoside-resistant strains.

This research was supported by the Medical Research Service of the Veterans Administration and the Warner-Lambert Pharmaceutical Research Division, Ann Arbor, Mich.

We thank the Clinical Microbiology Laboratories of the Albany Medical Center and Albany Veterans Administration Medical Center for assistance in collecting bacterial isolates. Constance Bales aided us in the preparation of the manuscript.

LITERATURE CITED


