Comparative Activities of Aztreonam and Cefotaxime Against Escherichia coli and Bacteroides spp. in Pure and Mixed Cultures

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The activities of aztreonam and cefotaxime against one Escherichia coli strain and three Bacteroides strains have been studied by using pure and mixed cultures of aerobic and anaerobic bacteria. A fixed concentration (8 μg/ml) of cefotaxime or aztreonam killed E. coli that was exposed in pure culture, but the pressure of Bacteroides spp. in the same system deteriorated cefotaxime, allowing the full growth of E. coli after 24 h. On the other hand, the presence of Bacteroides spp. produced less deterioration of aztreonam, which reduced the initial E. coli inoculum. This observation could be useful in clinical practice when treating mixed aerobic and anaerobic infections.

Aztreonam (SQ 26,776) is a new synthetic antimicrobial agent belonging to the monobactam group of beta-lactams, and its activity is confined mainly to aerobic and facultative gram-negative bacilli, against which it possesses considerable potency, as well as possessing stability to beta-lactamases (2, 3, 5, 8). The activity of cefotaxime is better known, and it has shown excellent antimicrobial activity in vitro and in vivo against many microorganisms, especially aerobic and facultative gram-negative bacteria (1). Both aztreonam and cefotaxime have very little activity against Bacteroides fragilis (1, 2, 5, 8), so their antimicrobial spectra are, in some ways, very similar, although the lower susceptibility of aztreonam to the beta-lactamase produced by this organism (2, 5, 8) could be a major advantage compared to cefotaxime, especially in those clinical infections in which mixtures of aerobic and anaerobic flora are involved.

The aim of the present investigation was to study the in vitro activity of aztreonam and cefotaxime against Escherichia coli and Bacteroides spp. exposed in pure and mixed cultures, such as occur in many clinical infections.

MATERIALS AND METHODS

Bacterial strains. Three clinically isolated Bacteroides strains, two of B. fragilis (strains A and B) and one of Bacteroides vulgatus (strain C), were studied. E. coli ATCC 25922 was also used.

Antimicrobial agents. Cefotaxime and aztreonam were kindly supplied as dry powder with known potency by Hoechst and the Squibb Institute, respectively.

Antimicrobial susceptibility. The MICs of cefotaxime and aztreonam against Bacteroides spp. were determined by the agar dilution method in Wilkins-Chalgren medium (9) with two different inocula. In brief, bacteria were grown in enriched brucella broth (6), which was incubated at 37°C in GasPak jars for 24 h. The turbidity of the broth culture was adjusted to match half the density of a McFarland no. 1 standard, equivalent to ca. 5 × 10^7 CFU/ml. The inocula were diluted ca. 1:20, inoculated with a Steers replicator in two sets of plates containing serial twofold dilutions of each antibiotic, and then incubated at 37°C aerobically and anaerobically for 24 h. The final inocula were ca. 2.5 × 10^2 CFU per spot.

Kinetic studies. Kinetic studies were carried out in fluid medium by using enriched brucella broth (6). One drop from a Pasteur pipette from a 24-h culture of E. coli or Bacteroides spp. was added to a tube containing 5 ml of enriched brucella broth with a fixed concentration (8 μg/ml) of cefotaxime or aztreonam. This inoculum corresponded to a bacterial concentration of 1 × 10^7 to 8 × 10^7 CFU/ml. When mixed inocula were used, 24-h-old broth cultures of the two organisms (E. coli and Bacteroides strain A, B, or C) were mixed on a 1:1 basis, and one drop from a Pasteur pipette was used as inoculum. All the experiments were carried out in a state of anaerobiosis with GazPak jars and incubation at 37°C. Viable counts were performed initially and after 6 and 24 h of incubation by subcultures with a calibrated loop to blood agar plates incubated in a state of aerobicism for viable counts of E. coli and to amikacin (250 mg/liter)-blood agar incubated in a state of anaerobiosis for viable counts of Bacteroides spp.

RESULTS

Table 1 shows the MICs of aztreonam and cefotaxime against the three Bacteroides strains, with two different inocula. A very important inoculum effect was that, weight for weight, cefotaxime was more active than aztreonam. The MICs of these two drugs against E. coli were 0.12 μg/ml in a state of aerobicism. The respective MICs in a state of aerobicism were 0.12 μg/ml for aztreonam and 0.06 μg/ml for cefotaxime.

Figure 1 shows the data that was obtained in the kinetic studies of the E. coli population that was exposed to a fixed concentration (8 μg/ml) of aztreonam or cefotaxime in pure culture and combined with each of the Bacteroides strains. E. coli that was exposed alone to a fixed concentration of cefotaxime was killed very effectively, with an average decrease in inoculum of about 5 log_{10} CFU/ml occurring after 24 h of exposure. The same concentration of aztreonam acting on E. coli alone was also bactericidal, although this effect was less than that obtained with cefotaxime, with an

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average decrease in inoculum of about 3.5 log_{10} CFU/ml occurring after 24 h of exposure. Neither aztreonam nor cefotaxime suppressed the growth of any of the Bacteroides strains, but *E. coli* grew in the presence of cefotaxime when it was combined with any of the Bacteroides strains. This effect was not observed in the presence of aztreonam, which reduced the *E. coli* inoculum in the presence of Bacteroides strains, albeit to a lesser extent than when *E. coli* was exposed in pure cultures.

**DISCUSSION**

It is well known that aztreonam and cefotaxime are not very active against strains of *B. fragilis* and *B. vulgatus* but show very strong activity against *Enterobacteriaceae* and especially *E. coli*. Many human infections are produced by mixtures of aerobic and anaerobic flora, particularly in abdominal sepsis, in which *E. coli* plus *B. fragilis* are very often isolated. Onderdonk et al. (4) showed that in certain experimental circumstances, the early mortality in abdominal sepsis is due to the effect of the facultative bacteria, particularly *E. coli*, more than to the anaerobic bacterial flora. The use of an antibiotic that is very active against *E. coli*, such as aztreonam or cefotaxime, may be justified in many clinical infections, especially if no resistant strains, such as *Bacteroides* strains, are associated with the susceptible ones. In some mixed infections with aerobic and anaerobic bacterial flora, whether they are bacteriologically documented or not, cefotaxime might be useless not only against *Bacteroides* strains but also against *E. coli* strains due to the enzymatic degradation of the drug by the *Bacteroides* strains. It has been shown that some *Bacteroides* strains reduced in vitro pharmacological levels of cefotaxime, allowing the growth of very susceptible strains of *E. coli* that were included in the same system (7). This mechanism could

**FIG. 1.** *E. coli* viability in the presence of 8 μg of cefotaxime or aztreonam per ml. Symbols: ○, cefotaxime against *E. coli*; ●, cefotaxime against *E. coli* plus a *Bacteroides* strain; ▲, aztreonam against *E. coli*; ▲, aztreonam against *E. coli* plus a *Bacteroides* strain. Panels A, B, and C represent experiments with the same *E. coli* strain throughout but with three different *Bacteroides* strains (strains A, B, and C, respectively.) For clarity, the kinetic data for *Bacteroides* strains are not shown.
TABLE 1. MICs of aztreonam and cefotaxime against three Bacteroides strains

<table>
<thead>
<tr>
<th>Organism and inoculum size (CFU/spot)</th>
<th>MICs (µg/ml) of:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Aztreonam</td>
</tr>
<tr>
<td>B. fragilis (A)</td>
<td></td>
</tr>
<tr>
<td>5 x 10^2</td>
<td>512</td>
</tr>
<tr>
<td>5 x 10^3</td>
<td>16</td>
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<tr>
<td>B. fragilis (B)</td>
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</tr>
<tr>
<td>5 x 10^2</td>
<td>256</td>
</tr>
<tr>
<td>5 x 10^3</td>
<td>16</td>
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<tr>
<td>B. vulgatus (C)</td>
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</tr>
<tr>
<td>5 x 10^2</td>
<td>512</td>
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<td>5 x 10^3</td>
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make totally ineffective the action of cefotaxime in some clinical infections with mixtures of aerobic and anaerobic flora. The clinician must be aware of this possibility and ask for a complete bacteriological study of the specimen, trying not to miss the demonstration of the anaerobic flora.

Sykes et al. (8) showed that cefotaxime had a greater susceptibility to enzymes from B. fragilis than did aztreonam. On the other hand, Phillips et al. (5) showed that beta-lactamases from Bacteroides strains hydrolyzed aztreonam slowly, and Jacobus et al. (2) showed that clavulanic acid acted synergistically with this antibiotic against some B. fragilis strains. However, this effect was observed only in 5 of the 15 strains tested, which suggested either that some beta-lactamases from these organisms might be unaffected by clavulanic acid or that their resistance to aztreonam might be derived from other mechanisms (2). Our results seem to support the evidence for lower susceptibility of aztreonam to the beta-lactamases produced by Bacteroides strains, since each of the Bacteroides strains tested in our study allowed full growth of E. coli in the presence of cefotaxime, whereas none of the Bacteroides strains prevented the action of aztreonam against E. coli. Nevertheless, Bacteroides strains B and C slightly reduced the activity of aztreonam against E. coli.

On summary, although aztreonam is less active than cefotaxime against Bacteroides strains, its higher resistance, compared with cefotaxime, to the enzymes from these organisms may allow a high enough active concentration of the drug to kill susceptible E. coli strains in a mixed aerobic and anaerobic bacterial infection. On the other hand, the bactericidal effect of cefotaxime on E. coli can be suppressed if some Bacteroides strains are present in the same system. These results suggest that aztreonam may have an additional advantage over cefotaxime, and further investigations, especially with in vivo models of these experimental infections, should be worthwhile.

LITERATURE CITED