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# Comparative In Vitro Activity of Ceftizoxime, Cefoperazone, and Cefoxitin Against Anaerobic Bacteria

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Against 482 obligate anaerobes studied by the agar dilution technique, ceftizoxime was significantly more active than both cefoxitin and cefoperazone ($P < 0.001$); the latter two agents were comparable in activity. The enhanced activity of ceftizoxime, as compared with the activity of cefoxitin, was against both gram-positive and gram-negative anaerobes (especially *Lactobacillus* and *Bacteroides* spp.). Cefoperazone, however, was more active than cefoxitin against gram-positive anaerobes (particularly *Lactobacillus* spp.) but was less active than cefoxitin against gram-negative anaerobes (particularly *Bacteroides fragilis* and *Veillonella* spp.).

Ceftizoxime (FK-749) and cefoperazone are two newer cephalosporins with enhanced in vitro activity against a wide variety of gram-positive and gram-negative organisms, including nosocomial pathogens such as *Serratia* and *Enterobacter* spp. (6, 7). Both antimicrobial agents exhibit stability to beta-lactamase activity, although ceftizoxime has been reported to be more stable than cefoperazone to beta-lactamase hydrolysis (1, 9). Their in vitro activities against clinically important anaerobic bacteria, however, have not been extensively investigated (1, 3, 5, 7, 8). We report here the in vitro activities of ceftizoxime and cefoperazone against 482 isolates of anaerobic bacteria, as determined by an agar dilution technique; the activities of both agents were compared with that of cefoxitin. These isolates were obtained from hospitalized patients of Harbor-University of California at Los Angeles Medical Center and Vancouver General Hospital, British Columbia, Canada, during 1975 to 1980. Identification to the species level was carried out in prereduced, anaerobically sterilized media by the methods of Holdeman et al. (4). The isolates were stored in 20% skim milk and frozen at −75°C until ready for antimicrobial agent susceptibility testing. Susceptibilities to ceftizoxime, cefoperazone, and cefoxitin were determined in Wilkins-Chalgren media (Difco Laboratories, Detroit, Mich.) by the method of Sutter et al. (11), with minor modifications. Twofold serial dilutions of sensitivity powder were added, and the final antibiotic concentrations ranged from 0.25 to 128 μg/ml. A 48-h subculture of the test organism in prereduced, anaerobically sterilized thioglycolate broth was adjusted to a McFarland number 1 nephelometer standard (2), previously determined to approximate $10^6$ to $10^7$ organisms per milliliter, as determined by colony count in roll tubes and prereduced, anaerobically, sterilized media. Inocula (0.0025 ml) were delivered with a Steers replicator (10). Plates were incubated at 37°C in anaerobic jars after air had been evacuated and replaced with a gas mixture of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. Anaerobic, microaerophilic (incubated in candle jars), and aerobic plates without antibiotics were used for growth and contamination controls, and two reference strains (*Bacteroides fragilis* 3186 and *Clostridium perfringens* 3000) with known minimal inhibitory concentrations (MICs) were included in each test for determining reproducibility. All results were read at 48 h, and the MIC recorded was the lowest antibiotic concentration which yielded no visible growth. We compared the in vitro activities by geometric mean MICs, using the Student's $t$ test (two tailed) with a significance level of $P < 0.01$.

MICs of the control strains (*B. fragilis* 3186 and *C. perfringens* 3000) determined in 15 separate tests agreed with the modal MIC ± 1 $\log_2$ dilution from 87 to 100% for all three antibiotics studied. The antibiotic concentrations required to inhibit 50 ($MIC_{50}$) and 90% ($MIC_{90}$) of the strains and the MIC ranges of the study drugs are summarized in Table 1. Overall, ceftizoxime (geometric mean MIC, 1.13 μg/ml) was more active than cefoxitin (geometric mean MIC, 1.84

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TABLE 1. *Comparative in vitro activities of ceftizoxime, cefoxitin, and cefoperazone against anaerobic bacteria*

| Organism (no.) | Antibiotic | $MIC_{50}$ (μg/ml) | $MIC_{90}$ (μg/ml) | MIC range (μg/ml) |
|---|---|---|---|---|
| *Bacteroides fragilis* (31) | Ceftizoxime | 7.4 | 52 | 1->128 |
| | Cefoxitin | 12 | 16 | 8-32 |
| | Cefoperazone | 39 | >128 | 1->128 |
| *B. vulgatus* (19) | Ceftizoxime | 0.4 | 4 | 0.25-64 |
| | Cefoxitin | 3.1 | 13 | 0.25-8 |
| | Cefoperazone | 14 | 30 | 0.25->128 |
| *B. distasonis* (17) | Ceftizoxime | 0.4 | 16 | 0.25-64 |
| | Cefoxitin | 10 | 37 | 1-64 |
| | Cefoperazone | 18 | 90 | 0.25-128 |
| *B. thetaiotaomicron* (11) | Ceftizoxime | 15 | 46 | 0.25-64 |
| | Cefoxitin | 25 | 52 | 16-64 |
| | Cefoperazone | 58 | 114 | 8-128 |
| *B. ruminicola* (14) | Ceftizoxime | 6.7 | 41 | 0.25-64 |
| | Cefoxitin | 11 | 52 | 0.25-64 |
| | Cefoperazone | 26 | 41 | 0.25-128 |
| *B. corrodens* (10) | Ceftizoxime | <0.25 | 1.0 | 0.25->128 |
| | Cefoxitin | 0.5 | 1.5 | 0.25-2 |
| | Cefoperazone | <0.25 | 16 | 0.25->8 |
| *Other Bacteroides* spp. (23) | Ceftizoxime | 0.4 | 20 | 0.25->128 |
| | Cefoxitin | 2 | 22 | 0.25-32 |
| | Cefoperazone | 0.5 | 53 | 0.25-64 |
| *Fusobacterium* spp. (9) | Cefitzoxime | 0.7 | 35 | 0.25-64 |
| | Cefoxitin | 2.5 | 18 | 0.25-32 |
| | Cefoperazone | 0.7 | 26 | 0.25-128 |
| *Veillonella* spp. (14) | Ceftizoxime | 0.7 | 1.8 | 0.25-32 |
| | Cefoxitin | 0.5 | 2.5 | 0.25-4 |
| | Cefoperazone | 4.0 | 14 | 0.25-64 |
| *Peptostreptococcus* spp. (29) | Ceftizoxime | <0.25 | 2.0 | 0.25-64 |
| | Cefoxitin | <0.25 | 3.4 | 0.25-64 |
| | Cefoperazone | 0.3 | 2.0 | 0.25-64 |
| *Peptococcus* spp. (84) | Ceftizoxime | <0.25 | 1.0 | 0.25-64 |
| | Cefoxitin | <0.25 | 0.8 | 0.25-8 |
| | Cefoperazone | <0.25 | 1.4 | 0.25-8 |
| *Clostridium perfringens* (27) | Ceftizoxime | 0.7 | 2.3 | 0.25-8 |
| | Cefoxitin | 0.7 | 1.0 | 0.25-16 |
| | Cefoperazone | 0.3 | 2.7 | 0.25-4 |
| Other *Clostridium* spp. (26) | Ceftizoxime | 4.0 | 30 | 0.25-128 |
| | Cefoxitin | 8.0 | 43 | 0.25-64 |
| | Cefoperazone | 8.0 | 53 | 0.25-64 |
| *Bifidobacterium* spp. (9) | Ceftizoxime | <0.25 | 18 | 0.25-32 |
| | Cefoxitin | 0.7 | 70 | 0.25-128 |
| | Cefoperazone | <0.25 | 2.5 | 0.25-8 |
| *Eubacterium* spp. (19) | Ceftizoxime | 0.6 | 22 | 0.25-32 |
| | Cefoxitin | 3.4 | 8 | 0.25-16 |
| | Cefoperazone | 0.5 | 99 | 0.25->128 |
| *Actinomyces* spp. (8) | Ceftizoxime | 0.25 | 21 | 0.25-32 |
| | Cefoxitin | 0.5 | 40 | 0.25-64 |
| | Cefoperazone | 0.5 | 1.6 | 0.25-2 |
| *Propionibacterium* spp. (94) | Ceftizoxime | <0.25 | <0.25 | 0.25-1 |
| | Cefoxitin | <0.25 | 0.5 | 0.25-16 |
| | Cefoperazone | <0.25 | 0.4 | 0.25-1 |
| *Lactobacillus* spp. (38) | Ceftizoxime | 36 | 64 | 0.5->128 |
| | Cefoxitin | >128 | >128 | 1->128 |
| | Cefoperazone | 11 | 31 | 0.5-128 |

μg/ml) ($P < 0.001$), whereas cefoperazone (geometric mean MIC, 1.81 μg/ml) was comparable to cefoxitin. At concentrations readily achieved in serum for these antibiotics (16 μg/ml), similar cumulative percentages of the total number of isolates were inhibited by ceftizoxime (85%), cefoperazine (80%), and cefoxitin (85%).

Considerable variation in susceptibility was observed for each antibiotic among different genera or species of anaerobes tested. Among *Bacteroides* spp., *B. fragilis* was more resistant than *B. vulgatus* ($P < 0.001$) but more susceptible than *B. corrodens* ($P < 0.001$) and was comparable in activity to *B. ruminicola* for all three antibiotics. *B. fragilis* was more resistant than *B. distasonis* to ceftizoxime ($P < 0.001$), whereas *B. fragilis* was more susceptible than *B. thetaiotaomicron* ($P < 0.001$) to cefoxitin. Among anaerobic cocci, *Veillonella* spp. were more resistant than *Peptococcus* spp. ($P < 0.001$) to cefoperazone and cefoxitin, whereas no significant difference in resistance to ceftizoxime was noted. Among gram-positive bacilli, *C. perfringens* was consistently more susceptible than non-*perfringens* species of *Clostridia* to all three antibiotics ($P < 0.001$). Similarly, *Lactobacillus* spp. were consistently more resistant than other non-spore-forming anaerobic gram-positive bacilli (*Propionibacterium*, *Bifidobacterium*, *Eubacterium*, and *Actinomyces* spp.) to all three antibiotics ($P < 0.005$).

The comparative in vitro activities of these agents indicated that ceftizoxime was more active overall than cefoxitin ($P < 0.001$), and this enhanced activity was against both gram-positive (particularly *Lactobacillus* spp.) and gram-negative anaerobes (particularly *Bacteroides* spp.) ($P < 0.005$). Cefoperazone, on the other hand, was more active than cefoxitin against gram-positive anaerobes (particularly *Lactobacillus* spp.; $P < 0.001$) but was less active than cefoxitin against gram-negative anaerobes (particularly *B. fragilis* and *Veillonella* spp.; $P < 0.005$). The enhanced in vitro activities of these newer cephalosporins, particularly ceftizoxime, against a wide variety of anaerobic bacteria, coupled with their broadened activity against many aerobic organisms, offers considerable promise for their use in single-agent therapy for mixed aerobic-anaerobic infections. Controlled clinical trials are indicated.

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