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Activity of Cefmetazole against Anaerobic Bacteria

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The in vitro activity of cefmetazole versus that of other antimicrobial drugs was assessed against 374 clinical isolates of Bacteroides spp., Clostridium spp., and anaerobic gram-positive cocci. Compared with cefoxitin, cefmetazole showed good activity against Bacteroides fragilis, other Bacteroides species, and anaerobic cocci. It was somewhat less active than cefoxitin against Bacteroides thetaiotaomicron, B. ovatus, B. distasonis, and B. vulgatus and somewhat more active against Clostridium spp.

Cefmetazole is a new 7α-methoxy cephalosporin with a wide range of activity (6). Its spectrum is similar to that of cefoxitin, which is very effective against many clinically important anaerobes, especially organisms in the Bacteroides fragilis group (9, 10). In this study, we compared cefmetazole with cefoxitin, piperacillin, clindamycin, and metronidazole.

Antimicrobial agents were obtained as follows: cefmetazole and clindamycin, The Upjohn Co., Kalamazoo, Mich.; cefoxitin, Merck & Co., Inc., Rahway, N.J.; piperacillin, Lederle Laboratories, Pearl River, N.Y.; and metronidazole and penicillin G, Sigma Chemical Co., St. Louis, Mo. The breakpoints for resistance were ≥32 µg/ml for cefoxitin and cefmetazole, ≥64 µg/ml for piperacillin, ≥8 µg/ml for clindamycin and metronidazole, and ≥2 µg/ml for penicillin G.

The 374 organisms tested were recent clinical isolates from the Tufts-New England Medical Center or strains referred there from other hospitals. The following organisms were included: B. fragilis group (200 isolates), other Bacteroides spp. (75 isolates), Clostridium spp. (48 isolates), and anaerobic cocci (51 isolates). B. fragilis ATCC 25285 and Bacteroides thetaiotaomicron ATCC 29741 were included as controls. The isolates were identified by methods described in the Virginia Polytechnic Institute manual (4).

The MICs were determined by a modified agar dilution method (10) using brain heart infusion agar base supplemented with vitamin K (0.0005%) and 5% sheep erythrocytes. The anaerobic cocci and bile-negative Bacteroides species were tested on brucella agar base supplemented with vitamin K and 5% sheep erythrocytes. Both of these groups exhibit better growth on this medium. Broth cultures were adjusted to contain approximately 105 CFU/ml (B. fragilis group and Clostridium spp.) or 106 CFU/ml (other Bacteroides species and cocci) and inoculated with a Steers replicator. The density of the spot inoculum on the plate was approximately 106 or 105 CFU. The plates were incubated in an anaerobic chamber (Coy Laboratory Products, Ann Arbor, Mich.) for 48 h at 37°C. The MIC was defined as the lowest concentration of antibiotic showing no growth, a single colony, or a barely visible haze.

The effect of inoculum density on the activity of cefmetazole was compared with the effect on cefoxitin. Broth cultures were grown for 5 to 6 h to the density of a 3

McFarland turbidity standard, and MICs were determined using spot inoculum densities of 108 and 109 CFU/ml with B. fragilis group isolates (n = 14) and Clostridium spp. (14 isolates). Spot inoculum concentrations of 108 and 109 CFU were compared for the bile-negative Bacteroides species (13 isolates).

Time-kill curves were performed for six strains of the B. fragilis group by using a method previously described (5). Organisms were grown to a concentration of approximately 108 CFU/ml in BHIS (Scott Laboratories, Inc., Fiskeville, R.I.) and treated with a drug concentration equal to the MIC and 4× MIC. Bactericidal activity was defined by a thousandfold reduction from the original count.

The susceptibilities of the strains are summarized in Table 1. Using a breakpoint of ≥32 µg/ml for resistance, 33% of B. fragilis group isolates were resistant to cefmetazole while only 10% were resistant to cefoxitin. This is similar to findings of other investigators (2, 7), although the percentage of strains resistant to cefmetazole was higher in our study than in that of Del Bene et al. (2). Piperacillin, clindamycin, and metronidazole were also more active than cefmetazole against the B. fragilis group.

Different species within the B. fragilis group demonstrated various degrees of susceptibility to the antimicrobial agents. None of the strains was resistant to metronidazole. Both B. thetaiotaomicron and Bacteroides ovatus were generally susceptible to cefoxitin, at 91 and 83%, but were not susceptible to cefmetazole, at 37 and 8%. Several species within the B. fragilis group are not presented in Table 1 because only a few strains were tested. The results are stated as the number of strains susceptible to cefmetazole out of the total number of strains of the species tested: Bacteroides distasonis, three of nine; B. uniformis, two of five; and B. vulgatus, three of six. Cefoxitin, piperacillin, and clindamycin were also more active against these species, although two of five strains of B. uniformis were resistant to piperacillin.

Cefmetazole was as active as the other antimicrobial agents against the bile-negative Bacteroides species. The strains we tested were much more susceptible to cefmetazole, cefoxitin, and piperacillin than were those of Del Bene et al. (2). This compares with results of previous studies we have done (3, 10), as well as those of others (1, 8). There was no resistance among the anaerobic cocci to cefmetazole, cefoxitin, or metronidazole. There was some resistance to metronidazole found in the aerotolerant cocci. The activity
of cefmetazole against *Clostridium* spp. was better than that of cefoxitin or piperacillin but not as good as that of clindamycin, metronidazole, or piperacillin.

Neither cefmetazole nor cefoxitin showed an inoculum effect with the *B. fragilis* group or other *Bacteroides* species. Cefmetazole demonstrated a minimal inoculum effect against *Clostridium* spp., with 2 of 13 strains showing a significant change in the MIC. Both of these strains were susceptible at the lower inoculum densities (0.5 and 2 μg/ml) but resistant at the higher density (32 μg/ml).

Time-kill curves run on five strains from the *B. fragilis* group showed a static effect at the MIC of cefmetazole. At 6 h past the introduction of the drug, the viable count of organisms was within one 10-fold dilution of the 0-time count. One strain of *B. fragilis* was reduced by three 10-fold dilutions at 6 h. Thus, cefmetazole was bactericidal for this organism. When the concentration of cefmetazole was increased to four times the MIC, four of the six strains showed a cidal effect at 6 h and five of the strains showed a cidal effect at 24 h.

Cefmetazole showed good in vitro activity against *Bacteroides* spp., *Clostridium* spp., and anaerobic gram-positive cocci, but it was not as effective as other drugs against the *B. fragilis* group.
LITERATURE CITED