In Vitro Activities of MK-0826 and 16 Other Antimicrobials against Bacteroides fragilis Group Strains

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The activity of MK-0826, a new carbapenem, against 309 Bacteroides fragilis group strains was investigated and compared with that of 11 other β-lactam and 5 non-β-lactam agents. MK-0826 showed excellent activity (MICs ranged from ≤0.06 to 4 μg/ml). The new carbapenem may be useful in the treatment of mixed anaerobic infections involving B. fragilis group strains.

Bacteroides fragilis group organisms are the anaerobic bacteria most frequently isolated in clinical infections and among the most resistant of all anaerobes to antibiotics. During the last few decades, different surveys have noted increased resistance of this group to several β-lactam and other antianaerobic agents (1–4, 10, 12). MK-0826 (ertapenem; formerly L-749,345) is a new 1-methyl injectable carbapenem that is highly resistant to inactivation by many extended- and broad-spectrum β-lactamases. It has a broad and potent spectrum of activity against both aerobic and anaerobic bacteria (6–9, 14). MK-0826 possesses pharmacokinetic advantages over currently available carbapenems. It is stable in the presence of human dehydropeptidase and therefore does not require the addition of cilastatin. Moreover, MK-0826 has a significantly longer half-life than imipenem and meropenem, which allows single daily dosing.

The present study was undertaken to determine the in vitro activity of MK-0826 against 309 recently isolated B. fragilis group strains. This activity was compared with those of 11 other β-lactam agents and 5 non-β-lactam agents.

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A total of 309 nonduplicated clinical strains of the B. fragilis group collected from January 1998 to December 1999 at the Hospital Clínico San Carlos, Madrid, Spain, were tested (189 B. fragilis, 36 Bacteroides thetaiotaomicron, 36 Bacteroides uniformis, 18 Bacteroides distasonis, 10 Bacteroides vulgatus, 8 Bacteroides caccae, 7 Bacteroides ovatus, 3 Bacteroides eggerthii and 2 Bacteroides stercoris strains). Each organism was identified using the Rapid ID 32A system (bioMérieux, Marcy l’Etoile, France). Sources of the isolates included abdomen (48.7%), skin and soft tissue (42%), blood (5.8%), respiratory tract (0.9%), body fluid (1.3%), and female genital tract (1.3%). The majority (84.8%) of specimens showed mixed growth and yielded an average of 1.1 species of the B. fragilis group per specimen.

Standard laboratory powders were supplied as follows: MK-0826, imipenem, and cefoxitin, Merck Sharp & Dohme de España, S.A., Madrid, Spain; chloramphenicol, Zyma Farmacéutica, Barcelona, Spain; clindamycin, Pharmacia & Upjohn Co., Barcelona, Spain; trovafloxacin, Pfizer, Inc., New York, N.Y.; metronidazole, Aventis Pharma, S.A., Madrid, Spain; moxifloxacin, Bayer, Barcelona, Spain; cefminox, Tedec-Meiji Farma, Madrid, Spain; ceftotan and meropenem, Astra Zeneca S.A., Madrid, Spain; cefizoxime, amoxicillin, ticarcillin, and clavulanate, SmithKline Beecham S.A., Madrid, Spain; piperacillin and tazobactam, Wyeth Lederle, Pearl River, N.Y.

Susceptibility testing was performed by the agar dilution method according to the National Committee for Clinical Laboratory Standards (NCCLS) (11) with brucella blood agar. Approximately 10⁵ CFU/spot was inoculated using a Steers multipoint replicator. The plates were incubated at 35°C for 48 h in an anaerobic chamber. MICs were defined as the lowest concentration of antimicrobial agent that yielded either no growth or a marked change in the appearance of growth compared to that of the growth on the control plate. MICs were determined for the group as a whole and for individual species as well. Reference strains B. fragilis ATCC 25285 and B. thetaiotaomicron ATCC 29741 were used as controls.

Analysis of the species distribution showed higher proportions of B. uniformis and B. fragilis than reported by other studies (2, 10, 12). The comparative activities of MK-0826 and the other agents tested are summarized in Table 1. The activity of MK-0826 against B. fragilis group strains was similar to that of imipenem and meropenem (MICs ranged from ≤0.06 to 4 μg/ml). The majority (84.5%) of strains tested were inhibited by MK-0826 at ≤1 μg/ml; for 11.3 and 4.2% of isolates, MK-0826 MICs were 2 and 4 μg/ml, respectively. For B. fragilis strains, the MICs at which 50 and 90% of the isolates were inhibited (MIC50s and MIC90s, respectively) of both MK-0826 and imipenem were slightly lower than those for B. thetaiotaomicron, B. uniformis, and B. distasonis isolates.

According to the majority of published studies (1–3, 7, 12), metronidazole and chloramphenicol were active against all strains. Of the test strains, 38.8% were resistant to clindamycin. In this study, as reported by Aldridge et al. (2), B. fragilis exhibited slightly more resistance to clindamycin than B. thetaiotaomicron. By contrast, other published reports (3, 10, 12) described greater levels of resistance to clindamycin for B. thetaiotaomicron than for B. fragilis. B. uniformis was the species of the group which was most resistant to this antibiotic (47.2%). During the last 2 decades, the increasing incidence of...
clindamycin resistance among *B. fragilis* group organisms has been widely reported (1, 4, 10, 12). In our hospital this rate increased from 20% in 1982 (4) to almost 40% in the present study.

Moxifloxacin and trovafloxacin showed good in vitro activity against *B. fragilis* group organisms (MIC₉₀ of 2 and 4 μg/ml, respectively). As we have previously reported (5), trovafloxacin was 1 to 2 dilutions more active than moxifloxacin against the various species of the group. The highest MIC₉₀s of both quinolones were among those for *B. uniformis* strains (8 and 16 μg/ml, respectively).

Piperacillin-tazobactam was the most active of the β-lactam–β-lactamase inhibitor combinations tested, inhibiting all strains at ≤64 μg/ml. The remaining β-lactam–β-lactamase inhibitor...
combinations tested were active against nearly all isolates included in the study. The resistance rate for ampicillin-sulbactam among B. distasonis strains was 5.6%, a value significantly lower than that (23%) recently reported by Aldridge et al. (2). In the present study, resistance to carbapenems was not found, although in previous studies reported by our group (4, 5), such resistance has been detected but with a low incidence. MK-0826 showed better activity than cefoxitin and piperacillin. Of resistance has been detected but with a low incidence. MK-

Although in previous studies reported by our group (4, 5), such resistance has been detected but with a low incidence. MK-0826 showed better activity than cefoxitin and piperacillin. Of the β-lactams tested, the three carbapenems showed the lowest MIC₉₀ values (1 to 2 μg/ml). By comparison, the MIC₉₀ of cefoxitin and piperacillin were 32 and >256 μg/ml, respectively. Of the cephalosporins, cefoxitin was the most active. This antibiotic inhibited 54% of the strains at 8 μg/ml and 94.5% of strains at 32 μg/ml. As has been noted in different studies (1–3, 12, 13), we found marked differences in the activity of several agents against the various species in the B. fragilis group. B. fragilis strains were more susceptible to the cephalosporins, piperacillin, β-lactam–β-lactamase inhibitor combinations, and the fluoroquinolones tested than were the other species of the group.

To our knowledge, only two studies about the activity of MK-0826 against B. fragilis group organisms have been published (7, 14). The results of the present study agree with those reported previously by Goldstein et al. (7) and Wexler et al. (14) and confirm the potent activity of MK-0826 against these organisms. These findings, together with the broad antimicrobial spectrum of MK-0826 and its pharmacokinetic properties, suggest clinical potential for the treatment of mixed anaerobic infections caused by B. fragilis group organisms.

REFERENCES


