In Vitro Activities of a New Des-Fluoroquinolone, BMS 284756, and Seven Other Antimicrobial Agents against 151 Isolates of Eikenella corrodens

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The des-fluoroquinolone BMS 284756 was active in vitro against all 151 clinical strains of Eikenella corrodens at a MIC of \( \leq 0.25 \) \( \mu \)g/ml and was comparable in activity to moxifloxacin and levofloxacin. The MIC at which 90% of the isolates were inhibited by penicillin G was 2 \( \mu \)g/ml; MICs for 8.6% of the strains (13 of 151) were \( \geq 4 \) \( \mu \)g/ml, including for two beta-lactamase-producing isolates. Amoxicillin-clavulanate and ampicillin-sulbactam inhibited all strains at a MIC of \( \leq 1 \) \( \mu \)g/ml.

Eikenella corrodens, a capnophilic, fastidious, slow-growing, gram-negative rod, has been increasingly implicated in a variety of infections associated with the human oral flora (1–2, 4–6). It is part of the normal oral microbiota recovered in approximately 60% of plaque samples (1, 7) and has been associated with human periodontitis (21). E. corrodens may also be found on the surface of the tongue, tonsils, and buccal mucosa and in saliva. Humans may harbor more than one clonal type of E. corrodens in the oral cavity; the significance of this is presently unknown.

While little is known about the role of the virulence factors of E. corrodens in pathogenicity (1, 19), common E. corrodens-associated infections include oral alveolar abscesses, parotitis, sinusitis, osteomyelitis of the mandible, bacteremia, and endocarditis following dental manipulation (4, 12, 17, 22). A strong association between subgingival E. corrodens and Actinobacillus actinomycetemcomitans in juvenile periodontitis has also been suggested (16). A knowledgeable basis for therapeutic selection of appropriate antimicrobial agents is essential.

Eikenella corrodens has a somewhat peculiar antimicrobial susceptibility pattern, being susceptible to penicillin but resistant to penicillinase-resistant penicillins such as dicloxacinil, erythromycin, other macrolides, clindamycin, metronidazole, and aminoglycosides (8, 9). The fluoroquinolones have been previously shown to be active against E. corrodens (10), but most have limited activity against anaerobic bacteria which are frequent copathogens in oral flora-based infections. The new des-fluoroquinolone BMS 284756 has been reported to have improved anaerobic activity (3, 25).

The strains tested were previously isolated from human infections (respiratory and/or oral isolates, 54; human and animal bites, 29; soft-tissue wounds, 15; other sources, 49) and identified by standard criteria (11, 18). Isolates were gram-negative, capnophilic rods that were positive for oxidase, nitrate reductase, and ornithine decarboxylase. Negative reactions were observed for catalase, urease, lysine decarboxylase, arginine dihydrolase, esculin hydrolysis, indole production, and acidification of carbohydrates. Standard laboratory powders were supplied as follows: BMS 284756, Bristol Meyers Squibb, Princeton, N.J.; moxifloxacin, Bayer Corp., West Haven, Conn.; levofloxacin, R.W. Johnson Pharmaceutical Research Institute, Raritan, N.J.; penicillin G and doxycycline, Sigma Chemical Corp., St. Louis, Mo.; amoxicillin-clavulanate, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.; ampicillin-sulbactam, Pfizer Inc., New York, N.Y.; and cefoxitin, Merck & Co., West Point, Pa.

Susceptibility testing was performed as previously reported (8, 9). Brucella agar supplemented with hemin, vitamin K1, and laked sheep blood was the basal medium. There is no NCCLS reference method for testing E. corrodens, so we treated this fastidious organism according to the NCCLS reference method for anaerobic bacteria. Serial dilutions of antimicrobial agents were reconstituted according to the manufacturers’ instructions and added to the agar at various concentrations. The agar plates were inoculated with a Steers replicator (Craft Machine, Inc., Chester, Pa.), and an inoculum of \( 10^5 \) CFU/spot was used. Plates were incubated in 5% CO\(_2\) for 48 h at 37°C. The MIC was defined as the lowest concentration of agent that yielded no growth or a marked change in growth compared to that on the growth control plate. Control strains tested included Escherichia coli ATCC 25922 and Staphylococcus aureus ATCC 29213. Beta-lactamase activity was determined with penicillin-resistant strains by using only a chromogenic test (cefimase disk; BBL, Cockeysville, Md.).

The activities of the various agents tested are shown in Table 1. Because breakpoints specific for E. corrodens have not been defined, we used those for anaerobic bacteria for our approximations for some of the drugs. All isolates were inhibited by \( \leq 0.25 \) \( \mu \)g/ml BMS 284756 and moxifloxacin and \( \leq 0.06 \) \( \mu \)g/ml levofloxacin. The penicillin MIC for 9.3% of the isolates was \( \geq 4 \) \( \mu \)g/ml, including for two isolates that also produced beta-lactamase, for which penicillin MICs were 8 \( \mu \)g/ml. Doxycy-
cine relative resistance (MIC, >2 µg/ml) was found for 17.8% (27 of 151) of the strains. All isolates were susceptible to ampicillin-sulbactam (MIC at which 90% of the isolates were inhibited [MIC90], 1 µg/ml), amoxicillin-clavulanate (MIC90, 0.5 µg/ml), and cefotixin (MIC90, 2 µg/ml).

Oral infections involving E. corrodens are usually multibacterial and involve both oral streptococci and anaerobic bacteria. Many oral anaerobes, such as Prevotella and Porphyromonas species, produce beta-lactamases; consequently, penicillin may be inadequate therapy. In addition, approximately 20% of patients either are allergic to penicillin or have side effects that require the selection of alternative antimicrobial agents. Since susceptibility studies are infrequently performed with fastidious isolates such as E. corrodens, the clinician must rely on the published literature to offer a guide to both empirical and specific therapy.

E. corrodens has a unique antibiotic susceptibility profile (3, 8–10) as it is usually susceptible to beta-lactam antibiotics, such as penicillin and ampicillin, but is resistant to penicillinase-resistant penicillins, such as dicloxacillin. Penicillin-resistant strains of E. corrodens have been increasingly isolated from human clinical specimens (23, 24). The mechanisms of resistance have been either plasmid-mediated beta-lactamases similar to those found in Neisseria species (20) or a nonplasmid-mediated 2a (Bush-type) beta-lactamase (14). Lacroix and Walker (15) further noted that a periodontal strain (EC-38) not only produced beta-lactamase but also had a partial Tn3 transposon that encoded for streptomycin resistance. E. corrodens is usually resistant to first-generation cephalosporins (e.g., cephalaxin and cefazolin) but is susceptible to second- and third-generation agents (e.g., cefotixin and cefuroxime). E. corrodens strains carrying plasmids that confer resistance to tetracycline have been reported (13), and resistance to clindamycin and metronidazole is usual (15). Macrolide activity against E. corrodens has been reported as variable; the organism is usually resistant to erythromycin and clarithromycin but may be susceptible to azithromycin (10).

Our study notes a 10.4% (13 of 125 isolates) resistance of E. corrodens strains to penicillin, but none were resistant to ampicillin-sulbactam, amoxicillin-clavulanate, or cefotixin. Two of our isolates were beta-lactamase producers, but the mechanism of resistance in the other strains was not elucidated. We also found 17.8% relative resistance to doxycycline.

Since several of the newer fluoroquinolones and the des-fluoroquinolones, a new class of agents, are reported to have enhanced anaerobic activity (3, 10, 25), we were encouraged to find in our study that BMS 284756, moxifloxacin, and levofloxacin all had very good in vitro activity against E. corrodens. This in vitro activity makes them potentially clinically useful in treating infections that involve E. corrodens.

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REFERENCES


