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In Vitro Activity of Cefbuperazone Against Anaerobic Bacteria

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The in vitro activity of cefbuperazone was compared with that of cefoxitin, moxalactam, and piperacillin against 305 strains of anaerobic bacteria. Piperacillin was the most active overall, inhibiting 97% of all anaerobes tested at 128 μg/ml. Cefbuperazone had poor activity against the *Bacteroides fragilis* group and *Clostridium difficile* (43 and 0% susceptible, respectively) but good activity (90.5%) against all other anaerobic bacterial species tested.

The ever increasing introduction of β-lactam antibiotics into the antimicrobial market, along with expanded awareness of the importance of anaerobic bacteria in infectious diseases, has underlined the need for information on the efficacy of these agents against anaerobic bacteria (1). It is important to note that methodological differences between laboratories may affect the results; thus, it is difficult to draw conclusions from a number of studies unless the same techniques are used throughout.

In this report, the activity against anaerobic bacteria of cefbuperazone, a new semisynthetic parenterally administered cephamycin antibiotic, was compared with that of cefoxitin, moxalactam, and piperacillin, drugs commonly used in anaerobic infections.

All bacteria were randomly selected recent clinical isolates from the Veterans Administration Wadsworth Medical Center, Los Angeles. Bacteria were identified by using established procedures (2,3). MICs were determined by an agar dilution technique described previously (3), with brucella-laked blood agar and an inoculum size of 10^5 CFU. Plates were incubated in GasPak jars for 48 h at 37°C. MICs were defined as the lowest concentration of antimicrobial agent permitting no growth, one discrete colony, or a barely visible haze. Reference strains of *Bacteroides fragilis* (ATCC 25285) and *Bacteroides thetaiotaomicron* (ATCC 29741) were used as controls in each test. MICs of piperacillin to *B. fragilis* and *B. thetaiotaomicron* were within one dilution of 8 μg/ml and 32 μg/ml, respectively; MICs of cefoxitin were 8 to 16 μg/ml (to *B. fragilis*) and 32 to 64 μg/ml (to *B. thetaiotaomicron*); MICs of cefbuperazone were 4 to 8 μg/ml (to *B. fragilis*) and 64 to 128 μg/ml (to *B. thetaiotaomicron*); MICs of moxalactam were 1 to 2 μg/ml (to *B. fragilis*) and 8 to 64 μg/ml (to *B. thetaiotaomicron*). This variance with moxalactam has been observed before in our laboratory.

The results of these in vitro studies are summarized in Table 1. In terms of overall activity, piperacillin was the most active, inhibiting 97% of all anaerobic bacteria tested at its breakpoint of 128 μg/ml (8 of 88 strains of *B. fragilis* group species were resistant). Cefoxitin, moxalactam, and cefbuperazone (all at 32 μg/ml) were able to inhibit 82, 76, and 69% of all strains tested, respectively. These results for cefoxitin and moxalactam are in excellent agreement with other recent studies from our laboratory (4). Cefbuperazone had particularly poor activity against the *B. fragilis* group overall (43% susceptible) and *Clostridium difficile* (0% susceptible) but relatively good activity (90.5% susceptible) against all other species tested. Moxalactam and cefoxitin also displayed relatively poor activity (64 and 77% susceptible, respectively) against the *B. fragilis* group overall, although activity against the species *B. fragilis* itself was excellent (see below). Moxalactam and cefoxitin were inactive against *C. difficile* as noted in previous reports from our laboratory; moxalactam inhibited 83% and cefoxitin inhibited 90% of all other strains tested (excluding *C. difficile*).

Piperacillin was the only antimicrobial agent tested that was active against *C. difficile* and was the most active agent against other *Clostridium* species. Gram-positive, nonsporeforming rods were very susceptible to both piperacillin (100%) and cefoxitin (97%) and less so to both cefbuperazone and moxalactam (81%).

Considerable species variation in susceptibility patterns of the *B. fragilis* group was noted; thus, results are given for the individual species as well as for the group overall. Cefbuperazone, cefoxitin, and moxalactam inhibited 100% of the *B. fragilis* isolates at breakpoint levels; piperacillin inhibited 96% (one strain of *B. fragilis* had an MIC of 256 μg/ml). All of the agents tested except cefbuperazone had good activity against *Bacteroides vulgatus* as well. *B. thetaiotaomicron*, *Bacteroides ovatus*, and *Bacteroides distasonis* displayed considerable resistance to cefoxitin, moxalactam, and cefbuperazone, whereas the activity of piperacillin against all of the species of the *B. fragilis* group was fairly consistent.

All of the agents tested had good to excellent activity against other *Bacteroides* species, *Fusobacterium* species, and gram-positive cocci. Several strains of *Fusobacterium* exhibited very light growth with tiny visible colonies that persisted up to the highest concentration of antimicrobial agent tested with cefoxitin, cefbuperazone, and, to a lesser degree, moxalactam. We have reported on this phenomenon in earlier studies (4) and have obtained preliminary evidence to indicate that this growth may represent cell wall-deficient forms of *Fusobacterium*.

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TABLE 1. Susceptibilities of 305 isolates of anaerobic bacteria to cefbuperazone, moxalactam, cefoxitin, and piperacillin

Organism (no. of isolates)	Antimicrobial agent[a]	MIC (μg/ml)			% Susceptible at breakpoint[b]
		Range	50%	90%	
Bacteroides fragilis group (88)	Cfb	4–>256	64	>256	43
	Cef	4–256	32	64	77
	Mox	1–>256	16	128	64
	Pip	1–>256	16	128	91
Bacteroides fragilis (28)	Cfb	4–16	8	16	100
	Cef	16–32	16	32	100
	Mox	1–16	1	16	100
	Pip	8–256	16	128	96
B. thetaiotaomicron (18)	Cfb	64–>256	64	>256	0
	Cef	16–128	64	128	67
	Mox	4–256	32	64	33
	Pip	8–>256	256	>256	83
B. distasonis (13)	Cfb	16–>256	>256	>256	15
	Cef	16–128	32	64	62
	Mox	64–>256	64	256	15
	Pip	4–>256	16	>256	85
B. ovatus (16)	Cfb	32–>256	256	>256	6
	Cef	16–256	32	64	50
	Mox	4–>256	32	64	56
	Pip	16–>256	32	128	94
B. vulgatus (13)	Cfb	16–128	32	128	54
	Cef	4–128	16	32	92
	Mox	2–256	4	128	85
	Pip	8–>256	16	128	93
B. melaninogenicus (11)	Cfb	4–128	8	16	91
	Cef	1–32	8	16	100
	Mox	0.5–64	16	32	91
	Pip	1–64	16	32	100
Other *Bacteroides* species[c] (10)	Cfb	0.5–64	16	32	90
	Cef	≤.06–32	8	32	100
	Mox	≤.06–64	1	8	90
	Pip	0.5–64	2	32	100
Fusobacterium spp.[d] (27)	Cfb	0.25–64	2	16	96
	Cef	0.25–16	0.5	8	100
	Mox	0.5–32	2	16	100
	Pip	0.06–128	1	64	100
Clostridium difficile (27)	Cfb	64–256	256	256	0
	Cef	64–256	128	256	0
	Mox	32–256	64	256	4
	Pip	4–32	8	16	100
Other *Clostridium* species[e]	Cfb	1–256	8	128	72
	Cef	2–128	4	64	80
	Mox	0.5–256	16	128	83
	Pip	0.25–32	1	16	100
Nonsporeforming, gram-positive rods[f] (32)	Cfb	0.25–256	4	64	81
	Cef	0.125–64	4	16	97
	Mox	0.06–256	4	256	81
	Pip	0.06–32	1	32	100
Gram-positive cocci[g] (81)	Cfb	0.06–64	2	8	97
	Cef	0.06–16	1	2	100
	Mox	0.06–128	2	8	97
	Pip	0.06–8	0.125	1	100

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TABLE 1—*Continued*

Organism (no. of isolates)	Antimicrobial agent[a]	MIC (μg/ml)			% Susceptible at breakpoint[b]
		Range	50%	90%	
Total (306)	Cfb				69
	Cef				82
	Mox				76
	Pip				97

[a] Abbreviations: Cfb, cefbuperazone; Cef, cefoxitin; Mox, moxalactam; and Pip, piperacillin.
[b] Based on FDA-approved package inserts: cefbuperazone, 32 μg/ml; cefoxitin, 32 μg/ml; piperacillin, 128 μg/ml; and moxalactam, 32 μg/ml.
[c] Susceptibility tested for two isolates of *Bacteroides oralis*, one isolate of *B. disiens*, one isolate of *B. gracilis*, two isolates of *B. bivius*, one isolate of *B. denticola*, and three isolates of *B. oris-buccae* group.
[d] Susceptibility tested for 18 *Fusobacterium nucleatum* isolates, 7 *F. varium* isolates, and 2 *F. necrophorum* isolates.
[e] Susceptibility tested for 10 *Clostridium perfringens* isolates, 5 *C. innocuum* isolates, 3 *C. subterminale* isolates, 9 *C. ramosum* isolates, and 3 *C. tertium* isolates.
[f] Susceptibility tested for 8 *Lactobacillus* isolates, 9 *Eubacterium* isolates, 13 *Actinomyces* isolates, and 2 *Bifidobacterium* isolates.
[g] Susceptibility tested for 18 *Peptostreptococcus magnus* isolates, 16 *P. prevotii* isolates, 13 *P. asaccharolyticus* isolates, 13 *P. variabilis* isolates, 8 *P. micros* isolates, and 13 *P. anaerobius* isolates.

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