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NOTES

Susceptibility of Anaerobic Bacteria to ALP 201

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The activity of ALP 201 against 350 strains of anaerobic bacteria was determined by an agar dilution method. Its activity was compared with those of piperacillin, cefoxitin, imipenem, clindamycin, metronidazole, and chloramphenicol. ALP 201 and imipenem were the most active agents tested. Based on these results, ALP 201 appears to be a promising antimicrobial agent for anaerobic infections and warrants further clinical investigations.

ALP 201 is a new penem antibiotic from Astra Clinical Research Center (Södertälje, Sweden). The purpose of the present study was to determine the in vitro activity of ALP 201 against a variety of anaerobic bacteria recently isolated from human infections. Its activity was compared with those of piperacillin, cefoxitin, imipenem, clindamycin, metronidazole, and chloramphenicol.

The strains tested were isolated from a variety of clinical specimens submitted to the National Bacteriological Laboratory and the Huddinge University Hospital, Stockholm, Sweden, during 1987 and 1988.

All strains were identified by the criteria of Holdeman et al. (2). The antimicrobial susceptibility tests were performed by the method of Dornbusch et al. (1). The strains were grown in rubber-stoppered tubes containing prereduced chopped meat broth with glucose. The antimicrobial susceptibility testing was performed on PDM-ASM agar (AB Biodisk, Solna, Sweden), with the addition of 5% defibrinated horse blood, by the agar dilution method. Inocula were 48-h cultures diluted 10^{-2} in prereduced Proteose Peptone broth (Difco Laboratories, Detroit, Mich.). This dilution resulted in 10^5 CFU per spot, when the bacteria were applied with a modified Steers replicator to freshly prepared agar plates containing the appropriate antimicrobial agent. An agar plate without an antimicrobial agent was always included as a growth control. The plates were read after 48 h of incubation at 37°C in anaerobic jars (GasPak; BBL Microbiology Systems, Cockeysville, Md.). The MIC was defined as the lowest concentration of the drug that inhibited growth. The appearance of a single colony or of a barely visible haze was disregarded. The presence of β-lactamase was determined by the nitrocefin disk assay.

The break points (in milligrams per liter) for the following antimicrobial agents were used with the recommendations given by the National Committee for Clinical Laboratory Standards (2a): piperacillin, 128; cefoxitin, 16; imipenem, 8; clindamycin, 2; metronidazole, 16; and chloramphenicol, 16.

The following antimicrobial agents were obtained from the indicated manufacturers: piperacillin, Lederle Laboratories (Wayne, N.J.); cefoxitin and imipenem, Merck Sharp & Dohme (Rahway, N.J.); clindamycin, The Upjohn Co. (Kalamazoo, Mich.); metronidazole, Leo Rhodia (Helsingborg, Sweden); chloramphenicol, Parke, Davis & Co. (Morris Plains, N.J.).

The in vitro activities of the antimicrobial agents against anaerobic cocci are shown in Table 1. All strains were susceptible to ALP 201, piperacillin, cefoxitin, and imipenem. All isolates were also susceptible to clindamycin, metronidazole, and chloramphenicol. One *Peptococcus magnus* strain produced β-lactamase.

Table 1 also shows the activities of the antimicrobial agents tested against *Propionibacterium acnes* strains. Imipenem and clindamycin were the most active agents tested. These drugs were more active against *Propionibacterium acnes* than were ALP 201, piperacillin, cefoxitin, and chloramphenicol. All strains were resistant to metronidazole.

All *Clostridium perfringens* strains were susceptible to ALP 201, piperacillin, cefoxitin, imipenem, clindamycin, metronidazole, and chloramphenicol (Table 1).

All *Clostridium difficile* isolates were susceptible to ALP 201, piperacillin, imipenem, metronidazole, and chloramphenicol (Table 1). A total of 50% of the strains required 64 mg of cefoxitin per liter to be inhibited, and for inhibition of 90% of the isolates, 128 mg/liter was required. The MIC of clindamycin for 50% of strains tested was 4.0 mg/liter, and the MIC of clindamycin for 90% of the strains tested was 8.0 mg/liter.

ALP 201 and imipenem were the most active beta-lactams tested against *Bacteroides fragilis* strains (Table 1). Cefoxitin also inhibited most of these strains (MIC for 90% of strains tested, 16.0 mg/liter). Most of the strains were susceptible to piperacillin and clindamycin, whereas all of them were susceptible to metronidazole and chloramphenicol. Of 100 *B. fragilis* strains tested, 89 produced β-lactamases.

All of the other *Bacteroides* strains were susceptible to the beta-lactams tested (Table 1). ALP 201, imipenem, and clindamycin showed the highest antimicrobial activities. Piperacillin, cefoxitin, and chloramphenicol were active against all *Bacteroides* species tested. A few *Bacteroides* isolates (*B. asaccharolyticus*, one strain; *B. bivius*, two strains; and *B. ruminicola*, one strain) were resistant to metronidazole. Fifteen strains produced β-lactamases.

All fusobacteria were susceptible to the beta-lactam antibiotics tested (Table 1). Most strains showed low MICs of clindamycin, metronidazole, and chloramphenicol.

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TABLE 1. In vitro activities of ALP 201 and other antimicrobial agents against anaerobic bacteria

Microorganisms (no. of isolates)	Antimicrobial agent	MIC (mg/liter)[a]			% Resistant[b]
		Range	50%	90%	
Anaerobic cocci (50)[c]	ALP 201	0.008–4.0	0.125	4.0	
	Piperacillin	0.016–2.0	0.125	0.25	0
	Cefoxitin	0.064–8.0	1.0	4.0	0
	Imipenem	0.016–0.064	0.032	0.064	0
	Clindamycin	0.016–1.0	0.064	0.064	0
	Metronidazole	0.125–8.0	4.0	4.0	0
	Chloramphenicol	0.25–8.0	2.0	8.0	0
Propionibacterium acnes (30)	ALP 201	0.064–8.0	0.064	2.0	
	Piperacillin	0.125–0.25	0.25	0.25	0
	Cefoxitin	0.125–1.0	0.125	0.25	0
	Imipenem	0.032–0.064	0.032	0.064	0
	Clindamycin	0.016–0.064	0.016	0.032	0
	Metronidazole	32–≥64	≥64	≥64	100
	Chloramphenicol	1.0	1.0	1.0	0
Clostridium perfringens (30)	ALP 201	0.25–0.5	0.5	0.5	
	Piperacillin	0.016–2.0	0.064	1.0	0
	Cefoxitin	0.5–1.0	0.5	1.0	0
	Imipenem	0.016–0.5	0.125	0.5	0
	Clindamycin	0.008–1.0	0.125	1.0	0
	Metronidazole	1.0–4.0	1.0	1.0	0
	Chloramphenicol	4.0–8.0	4.0	4.0	0
Clostridium difficile (50)	ALP 201	2.0–8.0	4.0	8.0	
	Piperacillin	0.125–8.0	4.0	4.0	0
	Cefoxitin	64–128	64	128	100
	Imipenem	8.0	8.0	8.0	0
	Clindamycin	0.5–128	4.0	8.0	55
	Metronidazole	0.125–0.25	0.125	0.25	0
	Chloramphenicol	0.125–4.0	4.0	4.0	0
Bacteroides fragilis group[d] (100)	ALP 201	0.032–2.0	0.125	0.25	
	Piperacillin	1.0–128	4.0	64	0
	Cefoxitin	2.0–32	8.0	16.0	8
	Imipenem	0.064–0.5	0.064	0.5	0
	Clindamycin	0.016–8.0	0.5	2.0	2
	Metronidazole	0.25–2.0	0.5	1.0	0
	Chloramphenicol	0.5–8.0	4.0	4.0	0
Other *Bacteroides* spp.[e] (50)	ALP 201	0.008–0.25	0.064	0.125	
	Piperacillin	0.064–8.0	1.0	4.0	0
	Cefoxitin	0.125–1.0	0.5	1.0	0
	Imipenem	0.016–0.25	0.032	0.032	0
	Clindamycin	0.016–0.25	0.016	0.016	0
	Metronidazole	0.064–64	1.0	1.0	8
	Chloramphenicol	4.0	4.0	4.0	0
Fusobacterium spp.[f] (40)	ALP 201	0.008–0.25	0.125	0.125	
	Piperacillin	0.016–1.0	0.064	0.064	0
	Cefoxitin	0.064–16.0	0.5	0.5	0
	Imipenem	0.008–0.064	0.032	0.064	0
	Clindamycin	0.016	0.016	0.016	0
	Metronidazole	0.25–4.0	4.0	4.0	0
	Chloramphenicol	0.032–4.0	4.0	4.0	0

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[b] Strains were classified as resistant when the MIC was greater than the break-point concentration.
[c] Includes *Peptococcus asaccharolyticus*, *Peptococcus indolicus*, *Peptococcus magnus*, *Peptococcus prevotii*, *Peptostreptococcus anaerobius*, *Peptostreptococcus micros*, and *Peptostreptococcus parvulus*. One strain produced β-lactamase.
[d] Includes *B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*, and *B. uniformis*. Of 100 strains, 89 were β-lactamase producers.
[e] Includes *B. asaccharolyticus*, *B. bivius*, *B. disiens*, *B. intermedius*, *B. melaninogenicus*, and *B. ruminicola*. Of 50 strains, 15 were β-lactamase producers.
[f] Includes *F. nucleatum*, *F. mortiferum*, and *F. varium*.

The in vitro data presented here indicate that ALP 201 is a promising new antimicrobial agent which may be useful in the treatment and prophylaxis of anaerobic infections. The antimicrobial susceptibility patterns of the tested anaerobic bacteria were rather similar to the findings by other laboratories in different countries (4). In planning the therapy of an infection which appears to be caused by anaerobic bacteria, it is appropriate to consider that most infections are caused by

both anaerobic and aerobic bacteria (3). Therefore, antimicrobial agents such as ALP 201, which are effective against both anaerobes and aerobes (data on file, Astra Clinical Research Centre), may be useful, especially in the treatment of intra-abdominal infections and genital tract infections in females. ALP 201 is a promising agent that warrants further investigations to determine whether it will be useful in the antimicrobial therapy of anaerobic infections.

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