ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1988, p. 584–586
0066-4804/88/040584-03$02.00/0

Vol. 32, No. 4

Activity of Trospectomycin against *Bacteroides fragilis* and Other *Bacteroides* Species

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The in vitro activity of trospectomycin (U-63366; 6′-*n*-propyl spectinomycin pentahydrate sulfate) was evaluated against 189 clinical isolates of the *Bacteroides fragilis* group and 65 *Bacteroides* species isolates. At ≤8 μg/ml, the activity of trospectomycin compared favorably with those of clindamycin and cefoxitin against *B. fragilis*, *Bacteroides distasonis*, and *Bacteroides vulgatus*, and there was no cross resistance to these three drugs among the strains of the *B. fragilis* group. All the *Bacteroides* species were susceptible to trospectomycin. The results of this in vitro study indicate that trospectomycin possesses excellent activity against *Bacteroides* species.

Trospectomycin (U-63366; 6′-*n*-propyl spectinomycin pentahydrate sulfate) is a new parenteral amino-cyclitol similar in structure to spectinomycin. It acts by binding to the 30S ribosome and inhibits protein synthesis. It has excellent activity against many gram-positive bacteria, *Neisseria gonorrhoeae*, and *Haemophilus ducreyi* (5, 6; K. Rolston, P. Thirolf, and D. H. Ho, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 205, 1985). Its activity against chlamydiae and mycoplasmas is being investigated (A. L. Laborde and R. J. Mourey, 27th ICAAC, abstr. no. 266, 1987). In a preliminary study, performed in our laboratory, it demonstrated very good in vitro activity against 30 strains of *Bacteroides fragilis*. Hence, if this agent is proven to exhibit good activity against other *Bacteroides* species which are prominent pathogens in suppurative infections of the female genital tract it should be very useful in the management of many sexually transmitted diseases and pelvic inflammatory disease. In addition, it could possibly be useful as one of the agents in the treatment of mixed anaerobic-aerobic infections. To evaluate the potential of the drug, we studied the in vitro activity of trospectomycin against 254 strains of the genus *Bacteroides* and compared its activity with that of six other antimicrobial agents which could be used for the treatment of such conditions. The bacteria were recent clinical isolates from New England Medical Center or referrals from medical centers in the United States. Included were 189 *B. fragilis* group isolates (11 *B. distasonis*, 114 *B. fragilis*, 18 *B. ovatus*, 25 *B. thetaiotaomicron*, and 21 *B. vulgatus* isolates) and 65 *Bacteroides* species isolates. The *Bacteroides* species were divided into three groups. One group comprised 34 isolates of *B. bivius* and *B. disiens*, which are considered mainly to be pathogens of the female pelvis and genital tract. The second group consisted of 16 isolates of *Bacteroides* species frequently associated with oral and dental infections and which are referred to here as oral bacteroides. The following species were included within this group: *Bacteroides asaccharolyticus*, *B. intermedius*, *B. oris-B. buccae*, *B. loeschii*, and *B. melaninogenicus*. The third group consisted of 15 isolates from species not included in the two groups described above (12 with nonconclusive identifications and 3 *B. ureolyticus* isolates) and is referred to as "other *Bacteroides* species." All the isolates were identified by the procedures outlined in the *Anaerobe Laboratory Manual*, Virginia Polytechnic Institute (3). Standard powders of the antimicrobial agents were supplied by the manufacturers as follows: trospectomycin and clindamycin, The Upjohn Co., Kalamazoo, Mich.; ampicillin and doxycycline, Sigma Co., St. Louis, Mo.; cefoxitin, Merck Sharp & Dohme, Rahway, N.J.; and cefaclor, Eli Lilly & Co., Indianapolis, Ind. Stock solutions of the standard antibiotic powders were prepared in distilled water at 10 times the highest concentration of antibiotic tested and kept frozen at −70°C until ready to be used.

MICs were determined by a modified agar dilution technique using a Steers replicator to apply the inocula (10). The medium used was brain heart infusion agar supplemented with 5% lysed sheep erythrocytes and vitamin K (0.0005%). The inocula were prepared from logarithmic-phase cultures in brain heart infusion supplemented with 0.005% hemin and 0.0005% vitamin K. With the rapidly growing *B. fragilis* group isolates, logarithmic phase was achieved in 5 to 6 h of incubation, while the *Bacteroides* species isolates required overnight incubation. The cultures were adjusted to contain approximately 10^7 CFU/ml; consequently, approximately 10^4 bacteria per spot were delivered to the plate surface. Reference strains *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *B. melaninogenicus* TAL 7846 were used as controls with each test performed. Once inoculated, the plates were incubated in an anaerobic chamber at 37°C for 48 h. The MICs were read as the lowest concentrations of antimicrobial agent that completely inhibited growth, disregarding a single colony or a faint haze.

The results of susceptibility testing of all the isolates are shown in Table 1. Trospectomycin exhibited consistently good activity against the *B. fragilis* group, comparable to that of clindamycin and cefoxitin. Interestingly, there was no cross resistance among these three drugs with any of the *B. fragilis* group isolates included in this study. An analysis of susceptibilities by species revealed that trospectomycin had excellent activity against *B. distasonis*, *B. fragilis*, and *B.*

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TABLE 1. Susceptibility of *Bacteroides* isolates

Bacterium (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		% Resistant[b]
		Range	90%	
Bacteroides fragilis group (189)	Trospectomycin	1.0–64.0	4.0	7.0
	Clindamycin	0.06–>16.0	2.0	5.0
	Ampicillin	1.0–>64.0	>64.0	93.0
	Doxycycline	0.12–>64.0	32.0	40.0
	Cefoxitin	1.0–128.0	16.0	8.0
	Cefaclor	16.0–>64.0	>64.0	100.0
Bacteroides distasonis (11)	Trospectomycin	1.0–4.0	2.0	0
	Clindamycin	≤0.12–16.0	0.5	9.0
	Ampicillin	4.0–>64.0	32.0	90.0
	Doxycycline	≤0.25–16.0	16.0	40.0
	Cefoxitin	8.0–32.0	32.0	18.0
	Cefaclor	≥64.0	>64.0	100.0
Bacteroides fragilis (114)	Trospectomycin	1.0–16.0	4.0	6.0
	Clindamycin	≤0.12–>16.0	1.0	3.0
	Ampicillin	2.0–>64.0	>64.0	96.0
	Doxycycline	≤0.25–>64.0	64.0	65.0
	Cefoxitin	2.0–128.0	16.0	5.0
	Cefaclor	≥64.0	>64.0	100.0
Bacteroides ovatus (18)	Trospectomycin	1.0–64.0	8.0	17.0
	Clindamycin	0.25–>16.0	2.0	6.0
	Ampicillin	16.0–>64.0	>64.0	100.0
	Doxycycline	≤0.25–32.0	32.0	56.0
	Cefoxitin	8.0–128.0	32.0	18.0
	Cefaclor	≥64.0	>64.0	100.0
Bacteroides thetaiotaomicron (25)	Trospectomycin	1.0–64.0	8.0	22.0
	Clindamycin	≤0.12–16.0	4.0	3.0
	Ampicillin	16.0–>64.0	>64.0	100.0
	Doxycycline	≤0.25–64.0	32.0	36.0
	Cefoxitin	8.0–32.0	16.0	3.0
	Cefaclor	≥64.0	>64.0	100.0
Bacteroides vulgatus (21)	Trospectomycin	1.0–4.0	4.0	0
	Clindamycin	≤0.12–16.0	1.0	8.0
	Ampicillin	0.5–>64.0	>64.0	95.0
	Doxycycline	≤0.25–>64.0	16.0	48.0
	Cefoxitin	2.0–16.0	16.0	0
	Cefaclor	16.0–>64.0	>64.0	95.0
Bacteroides species (65)	Trospectomycin	0.25–4.0	2.0	0
	Clindamycin	≤0.12–1.0	0.25	0
	Ampicillin	0.25–>64.0	64.0	49.0
	Doxycycline	0.25–>64.0	64.0	50.0
	Cefoxitin	0.25–16.0	8.0	0
	Cefaclor	1.0–>64.0	>64.0	57.0
Bacteroides bivius-B. disiens (34)	Trospectomycin	0.5–4.0	2.0	0
	Clindamycin	≤0.12–0.5	≤0.12	0
	Ampicillin	≤0.25–>64.0	32.0	48.0
	Doxycycline	0.5–>64.0	64.0	55.0
	Cefoxitin	≤0.25–8.0	2.0	0
	Cefaclor	0.5–>64.0	>64.0	61.0
Oral bacteroides (16)	Trospectomycin	≤0.25–4.0	2.0	0
	Clindamycin	≤0.12–0.25	≤0.12	0
	Ampicillin	≤0.25–>64.0	>64.0	46.0
	Doxycycline	≤0.25–64.0	64.0	46.0
	Cefoxitin	≤0.25–8.0	8.0	0
	Cefaclor	1.0–>64.0	>64.0	50.0
All other *Bacteroides* species (15)	Trospectomycin	≤0.25–1.0	2.0	0
	Clindamycin	≤0.12–1.0	0.5	0
	Ampicillin	≤0.25–32.0	32.0	53.0
	Doxycycline	≤0.25–>64.0	16.0	40.0
	Cefoxitin	≤0.25–16.0	8.0	0
	Cefaclor	≤0.25–>64.0	>64.0	60.0

[a] 90%, MIC for 90% of isolates tested.
[b] Breakpoints for resistance: trospectomycin, ampicillin, doxycycline, and cefaclor, >8 μg/ml; clindamycin, >4 μg/ml; cefoxitin, >16 μg/ml.

vulgatus and good-to-moderate activity against *B. ovatus* and *B. thetaiotaomicron*. Our results also showed that between 90 and 100% of all the *B. fragilis* isolates were resistant to ampicillin and cefaclor and that approximately half of them were resistant to doxycycline. The rate of resistance to doxycycline among the *B. fragilis* isolates was lower than the overall nationwide rates of resistance to tetracycline that have been reported (>70%; 4, 9). The superior in vitro activity of doxycycline over that of tetracycline against *B. fragilis* was reported earlier by Sutter et al. (8).

Among other *Bacteroides* species, there was no resistance to trospectomycin, clindamycin, or cefoxitin. Resistance in the *Bacteroides* species was limited to ampicillin, doxycycline, and cefaclor. Approximately 50% of all the *Bacteroides* species isolates were resistant to these three drugs. The lack of activity of tetracycline and some β-lactam antibiotics against the *Bacteroides bivius-B. disiens* and oral bacteroides group was reported previously (1, 2, 7). However, our findings indicate even higher levels of resistance among these two groups of anaerobic bacteria than those formerly reported. The highest overall resistance in the "other *Bacteroides* species" group was due to three isolates of *B. ureolyticus*. This rapid increase in resistance compels a search for alternative antimicrobial agents against infections caused by these agents.

In summary, our results indicate excellent in vitro activity of trospectomycin against all *Bacteroides* isolates. Pharmacokinetic studies in human volunteers showed mean peak levels in serum of 81.2 μg/ml and a mean half-life of 2.2 h after intravenous injection of a 1,000-mg dose. This level in serum is 10 to 40 times higher than the MIC for 90% of all the *Bacteroides* isolates studied (A. Bye and L. G. Dring, 27th ICAAC, abstr. no. 272, 1987). These findings, coupled with its activity against gram-positive organisms, *N. gonorrhoeae*, and *H. ducreyi*, might make it a useful drug in the treatment of pelvic infections and a suitable alternative to penicillin or tetracycline in mixed anaerobic infections that have failed this type of therapy. However, to further assess the role of trospectomycin as a therapeutic agent for these serious conditions, information regarding its in vitro activity against anaerobic streptococci and clostridia, also important pathogens in gynecological infections, is needed. Additional animal experimentation and pharmacological information is also required.

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