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In Vitro Activities of Tigecycline against the *Bacteroides fragilis* Group

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The in vitro activities of tigecycline were tested against 831 isolates of the *Bacteroides fragilis* group representing all of the species within the group. On a weight-to-weight basis (8 μg/ml), tigecycline was more active than clindamycin, minocycline, trovafloxacin, and cefoxitin and less active than imipenem or piperacillin-tazobactam against all isolates of the *B. fragilis* group. Tigecycline geometric mean MICs were statistically higher against *B. distasonis* than other *Bacteroides* species (*P* value of 0.0001).

The use of tetracyclines against anaerobic or mixed infections has been limited by the increased resistance of anaerobic bacteria against this class of antibiotics. Tigecycline (GAR-936), a new glycylcycline derivative of minocycline, has shown excellent in vitro activities against a broad spectrum of aerobic bacteria containing tetracycline-resistant elements (2, 4, 7, 8, 13). Reports from the literature also show good antianaerobic activity, including against members of the *Bacteroides fragilis* group. These reports, however, included mostly isolates from the species *B. fragilis*, and the number of isolates from other species in the group was limited (2, 3, 7).

The *B. fragilis* group of bacteria are the most frequently isolated anaerobes from mixed infections and are also the most resistant (1, 9, 10). Resistance within the group is varied and has been related to specific drug-species combinations (10, 11). We undertook this study to determine the activity of tigecycline against the various species of the *B. fragilis* group.

Eight hundred thirty-one clinical *B. fragilis* group isolates (isolation dates from 1998 to 2000) representing the various species were tested. The isolates were referred for susceptibility testing to New England Medical Center by various medical centers in the United States as part of a continuing multicenter survey of resistance of the *B. fragilis* group (9, 10, 11). The medical centers represent different geographical areas so as to indicate overall resistance rate for the nation. The identification of all isolates was confirmed at the time of testing by using API Anident or standard methodology when applicable (5, 12). The following numbers of strains within these species were studied: *Bacteroides distasonis*, 98; *B. fragilis*, 289; *Bacteroides ovatus*, 90; *Bacteroides thetaiotaomicron*, 185; *Bacteroides uniformis*, 26; *Bacteroides vulgatus*, 86; and other *B. fragilis* group species, 57 (53 *B. caccae*, 1 *B. eggerthii*, 1 *B. merdae*, and 2 *B. stercoralis* strains).

The antimicrobial agents were provided by the manufacturers and included tigecycline, minocycline, and piperacillin-tazobactam from Wyeth Ayerst Research Laboratories, Pearl River, N.Y.; cefoxitin and imipenem from Merck and Company, West Point, Pa.; trovafloxacin from Pfizer Central Research, Groton, Conn.; and clindamycin from Pharmacia Upjohn, Kalamazoo, Mich.. The antimicrobials were prepared according to the manufacturers' instructions. Stock solutions at 10 times the desired test concentration were kept frozen at −70°C until the day of the test.

The MICs of the antibiotics were determined by the agar dilution method according to the procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (6). The antibiotic-containing plates were prepared on the day of the test with enriched brucella agar (brucella agar supplemented with 5% lysed defibrinated sheep erythrocytes and 1 μg of vitamin K per ml). The bacteria were grown to the logarithmic phase, and their turbidity was adjusted to that of a 0.5 McFarland standard (~10^8 CFU/ml). The inocula (~10^5 CFU per spot) were delivered to the surface of the agar with a Steers replicator. The plates were incubated at 35 to 37°C in an anaerobic chamber for 48 h. The MICs were read as the lowest concentration of the antibiotic agent that resulted in a marked change in growth compared to that on the control plate. *B. fragilis* ATCC 25285 and *B. thetaiotaomicron* ATCC 29741 were used as controls in all of the test runs. Because NCCLS has not established breakpoints for resistance for tigecycline or minocycline, the activities of these two agents are expressed as percentages of isolates for which the MICs were specific (1, 2, 4, 8, and 16 μg/ml). Resistance breakpoints for the comparative agents are those listed in the NCCLS guidelines: cefoxitin, ≥64 μg/ml; imipenem, ≥16 μg/ml; piperacillin-tazobactam, ≥128 μg/ml; and clindamycin and trovafloxacin, ≥8 μg/ml (6).

The results of the evaluation are shown on Table 1. At a MIC of 8 μg/ml, 89.7% of the isolates were inhibited by tigecycline, while only 39.2% were inhibited by minocycline. At the same concentration, tigecycline inhibited a higher percentage of isolates than clindamycin or trovafloxacin (77.0%), while a higher concentration of cefoxitin (64 μg/ml) was needed to inhibit a comparable percentage (87.4%). Imipenem and piperacillin-tazobactam were the most active drugs in the evaluation. At their NCCLS-suggested breakpoints for resistance (16 μg/ml for imipenem and 128 and 4 μg/ml, respectively, for piperacillin and tazobactam in combination), there were no strains resistant to piperacillin-tazobactam and only one strain resistant to imipenem.

Analysis of the data by species showed that the MICs for *B. distasonis* were statistically significantly higher than those for

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TABLE 1. Activity of tigecycline and comparator agents against *B. fragilis* and related species

Species (no. of strains)	Antibiotic	MIC range (μg/ml)	MIC (μg/ml)[f]		% of isolates for which MIC (μg/ml) was[a]:					% Resistant[b]
			50	90	≥1	≥2	≥4	≥8	≥16	
B. distasonis (98)	Tigecycline	0.5–8	4	8	93.9	81.6	56.1	11.2	0	NA[c]
	Minocycline	0.25–32	8	16	81.6	76.5	74.5	56.1	20.4	NA
	Clindamycin	0.5–128	1	128						25.5
	Trovafloxacin	0.06–16	2	8						25.5
	TZP[d]	0.5–64	8	16						0
	Imipenem	0.125–16	1	2						1.0
	Cefoxitin	2–256	32	64						33.7
B. fragilis (289)	Tigecycline	0.25–32	2	8	86.9	56.7	19.4	10.0	4.8	NA
	Minocycline	0.25–64	8	32	81.7	79.6	77.5	67.1	45.7	NA
	Clindamycin	0.5–128	0.5	128						16.3
	Trovafloxacin	0.25–16	0.5	8						20.1
	TZP	0.5–64	1	4						0
	Imipenem	0.125–8	0.25	1						0
	Cefoxitin	2–128	16	32						3.5
B. ovatus (90)	Tigecycline	0.25–16	2	4	75.6	52.2	28.9	10.0	2.2	NA
	Minocycline	0.25–64	8	16	81.1	80.0	76.7	56.7	23.3	NA
	Clindamycin	0.5–128	2	128						31.1
	Trovafloxacin	0.5–16	2	8						14.4
	TZP	0.5–32	4	16						0
	Imipenem	0.125–4	0.25	1						0
	Cefoxitin	4–128	32	64						18.9
B. thetaiotaomicron (185)	Tigecycline	0.25–16	2	8	87.0	58.4	25.4	10.8	2.2	NA
	Minocycline	0.25–32	8	16	75.7	73.5	70.8	55.1	21.1	NA
	Clindamycin	0.5–128	2	128						27.0
	Trovafloxacin	0.5–32	1	8						22.7
	TZP	0.5–64	8	16						0
	Imipenem	0.125–4	0.5	1						0
	Cefoxitin	2–128	32	64						15.7
B. uniformis (26)	Tigecycline	0.25–8	1	2	65.4	34.6	3.8	3.8	0	NA
	Minocycline	0.25–32	8	16	80.8	76.9	76.9	57.7	19.2	NA
	Clindamycin	0.5–128	1	128						23.1
	Trovafloxacin	0.5–8	2	8						26.9
	TZP	0.5–16	2	16						0
	Imipenem	0.125–1	0.25	0.5						0
	Cefoxitin	2–32	16	32						0
B. vulgatus (86)	Tigecycline	0.5–8	1	4	75.6	43.0	17.4	7.0	0	NA
	Minocycline	0.25–32	8	16	74.4	73.3	72.1	64.0	25.6	NA
	Clindamycin	0.5–128	0.5	128						27.9
	Trovafloxacin	0.25–32	4	16						44.2
	TZP	0.5–32	4	8						0
	Imipenem	0.125–4	0.5	1						0
	Cefoxitin	4–128	8	64						10.5
Other Bacteroides spp. (57)[e]	Tigecycline	0.5–64	1	8	82.5	49.1	24.6	17.5	7.0	NA
	Minocycline	0.25–64	8	32	80.7	78.9	77.2	57.9	28.1	NA
	Clindamycin	0.5–128	1	128						19.3
	Trovafloxacin	0.125–16	1	8						14.0
	TZP	0.5–32	4	16						0
	Imipenem	0.125–4	0.25	1						0
	Cefoxitin	4–256	32	64						12.3
All *B. fragilis* group species combined (831)	Tigecycline	0.25–64	2	8	84.4	56.9	25.8	10.3	2.9	NA
	Minocycline	0.25–64	8	16	79.4	77.1	75.0	60.8	30.7	NA
	Clindamycin	0.5–128	1	128						23.0
	Trovafloxacin	0.06–32	1	8						23.0
	TZP	0.5–64	4	16						0
	Imipenem	0.125–16	0.5	1						0.1
	Cefoxitin	2–256	16	64						12.6

[a] NCCLS has not established breakpoints for resistance for tigecycline and minocycline.
[b] Resistance based on NCCLS-established breakpoints for fully resistant: cefoxitin, ≥64 μg/ml; clindamycin and trovafloxacin, ≥8 μg/ml; imipenem ≥16 μg/ml; piperacillin-tazobactam, ≥128 μg/ml.
[c] NA, not applicable.
[d] TZP, piperacillin-tazobactam.
[e] Includes 53 *B. caccae*, 1 *B. eggerthii*, 1 *B. merdae* and 2 *B. stercoralis* strains.
[f] 50 and 90, MIC_{50} and MIC_{90}, respectively.

the other *Bacteroides* species (*P* value of 0.0001 as calculated by a nonparametric Kruskal-Wallis test). The geometric mean MIC (MIC_{GM}) of 2.69 μg/ml was approximately twice the MIC_{GM} for the other species (data not shown in Table 1). The MIC range for this species, however, was not the highest. The highest MICs (32 and 64 μg/ml) were for one isolate each of *B. fragilis* and *B. caccae*, respectively. The lowest MICs at which 50 and 90% of the isolates tested are inhibited (MIC_{50} and MIC_{90}, respectively) for tigecycline were observed for *B. uniformis* (MIC_{50} of 1 μg/ml and MIC_{90} of 2 μg/ml). The MIC_{90}s for all other species were 8 μg/ml, with the exception of *B. ovatus* (MIC_{90} of 4 μg/ml).

The results of this evaluation show that tigecycline should be considered as a possible therapeutic agent for the treatment of mixed infections, particularly intra-abdominal sepsis. Clinical trials, in progress, should establish the potential use of this drug in mixed infections.

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