ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1999, p. 2320–2322 Vol. 43, No. 9
0066-4804/99/$04.00+0

Activities of New Antimicrobial Agents (Trovafloxacin, Moxifloxacin, Sanfetrinem, and Quinupristin-Dalfopristin) against *Bacteroides fragilis* Group: Comparison with the Activities of 14 Other Agents

CARMEN BETRIU,* MARÍA GÓMEZ, M. LUISA PALAU, ANA SÁNCHEZ, AND JUAN J. PICAZO

Servicio de Microbiología Clínica, Hospital Clínico San Carlos, 28040 Madrid, Spain

Received 11 March 1999/Returned for modification 13 May 1999/Accepted 29 June 1999

The antimicrobial activities of trovafloxacin, moxifloxacin, sanfetrinem, quinupristin-dalfopristin, and 14 other antimicrobial agents against 218 *Bacteroides fragilis* group strains were determined. A group of 10 imipenem-resistant strains were also tested. Imipenem, meropenem, and sanfetrinem had the lowest MICs of all of the β-lactams. Quinupristin-dalfopristin inhibited all of the strains at 2 μg/ml. Overall, the MICs of trovafloxacin and moxifloxacin for 90% of the strains tested were 1 and 2 μg/ml, respectively.

Increasing resistance of *Bacteroides fragilis* group bacteria to drugs commonly used in the treatment of anaerobic infections, such as several β-lactam agents or clindamycin, has been reported in the last 2 decades (5, 7, 10, 18, 19). Effective alternative antimicrobials with antianaerobic activity have become necessary. The older quinolones have a wide antibacterial spectrum and potential bactericidal activity against aerobic bacteria but have poor activity against anaerobes. Several newer quinolones, such as trovafloxacin and moxifloxacin, possess a broad antimicrobial spectrum which covers gram-positive and gram-negative bacteria. They are also effective against anaerobes. Sanfetrinem is the first member of a new class of tricyclic β-lactam compounds, the trinems (previously tribactams). Two publications (4, 9) have demonstrated that sanfetrinem possesses a broad spectrum of activity, which includes gram-negative and gram-positive aerobes and anaerobes, and exhibits high potency and stability against many β-lactamases. Quinupristin-dalfopristin is a semisynthetic injectable streptogramin with significant activity against gram-positive organisms and marked antianaerobic activity.

This study aimed to ascertain the current susceptibility pattern of these organisms in our hospital in order to detect trends and to evaluate the activities of the new agents. We compared the in vitro susceptibilities of recently isolated *B. fragilis* strains to both newer (moxifloxacin, trovafloxacin, sanfetrinem, and quinupristin-dalfopristin) and older antimicrobial agents (including β-lactam antibiotics, β-lactam–β-lactamase inhibitor combinations, and non-β-lactam agents).

(Part of this study was presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif., 24 to 27 September 1998.)

The 218 clinical isolates of *B. fragilis* group bacteria isolated in 1997 tested included the following numbers of isolates: *B. fragilis*, 133; *B. thetaiotaomicron*, 39; *B. uniformis*, 26; *B. caccae*, 6; *B. ovatus*, 6; *B. distasonis*, 4; and *B. vulgatus*, 4. A group of 10 *B. fragilis* strains (collected from 1989 to 1997) resistant to imipenem (MICs, 16 to >256 μg/ml) were also tested. Strains were identified by using the Rapid ID 32A system (bioMérieux, Marcy l'Etoile, France). Sources included skin and soft tissue (44.4%), abdomen (43.1%), blood (8.2%), respiratory tract (1.8%), body fluid (1.4%), female genital tract (0.9%), and bone (0.5%) samples.

Antimicrobial agents were obtained from the following companies: trovafloxacin, ampicillin, and sulbactam, Pfizer, New York, N.Y.; moxifloxacin, Bayer, Barcelona, Spain; sanfetrinem, Glaxo Wellcome, Verona, Italy; quinupristin-dalfopristin and metronidazole, Rhône-Poulenc Rorer, Madrid, Spain; chloramphenicol, Zyma Farmacéutica, Barcelona, Spain; clindamycin, Pharmacia & Upjohn, Barcelona, Spain; cefoxitin and imipenem, Merck Sharp & Dohme, West Point, Pa.; ceftizoxime, amoxicillin, ticarcillin, and clavulanate, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.; cefminox, Tedec-Meiji Farma, Madrid, Spain; piperacillin and tazobactam, Wyeth Lederle, Pearl River, N.Y.

MICs were determined by the agar dilution method in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines (15).

The results of susceptibility testing are presented in Table 1. Trovafloxacin displayed high levels of activity against members of the *B. fragilis* group, with 92 and 95% of the strains susceptible at 1 and 2 μg/ml, respectively. The in vitro activity of moxifloxacin was comparable to that of trovafloxacin, with 94% of all strains inhibited at 4 μg/ml. Trovafloxacin was slightly more active against *B. thetaiotaomicron* and *B. uniformis* than was moxifloxacin. Sanfetrinem showed excellent activity, inhibiting 99.5% of the strains at 4 μg/ml. The sanfetrinem MICs for 50 and 90% of the strains tested (MIC_{50} and MIC_{90}, respectively) were comparable to those of the carbapenems and lower than the MICs obtained with the other nine β-lactams tested. Overall, metronidazole and quinupristin-dalfopristin were the most active agents; both inhibited all strains at 2 μg/ml. For the cephamycins and piperacillin, there was variability in the susceptibility rates when MICs within 1 or 2 dilutions of the breakpoint were considered. Cefoxitin inhibited 70.6, 87.2, and 96.3% of the isolates at 16, 32, and 64 μg/ml, respectively. Within the group, *B. fragilis* strains were more susceptible to the cephalosporins tested than were the other species of the group. Cefoxitin and cefminox exhibited similar activities against *B. fragilis* strains, and ceftizoxime was markedly more active. In our hospital, the rate of resistance to clindamycin has remained at about 30 to 33% since 1994. We found one *B. fragilis* strain that was highly resistant to all of the β-lactam antibiotics, either alone or in combination with a β-lactamase inhibitor.

Metronidazole and chloramphenicol were uniformly effec-

* Corresponding author. Mailing address: Servicio de Microbiología Clínica, Hospital Clínico San Carlos, Plaza Cristo Rey s/n, 28040 Madrid, Spain. Phone: 341 3303486. Fax: 341 3303478. E-mail: cbetriu@efd.net.

TABLE 1. In vitro effectiveness of antimicrobial agents against the *B. fragilis* group

Organism (no. of strains tested) and antimicrobial	MIC[a] range	MIC_{50}[a]	MIC_{90}[a]	% Resistant strains[b]
B. fragilis group (218)				
Metronidazole	≤0.06–2	0.5	1	0
Chloramphenicol	0.1–8	4	4	0
Clindamycin	≤0.06–>256	0.5	>256	33.5
Cefoxitin	≤0.06–128	16	64	12.8
Ceftizoxime	≤0.06–>256	2	32	6.9
Cefminox	≤0.06–256	2	256	16.5
Cefotetan	≤0.06–>256	16	128	35.1
Piperacillin	≤0.06–>256	8	256	22.8
Imipenem	≤0.06–256	0.1	1	0.5
Meropenem	≤0.06–256	0.1	1	0.5
Amoxicillin-clavulanate	≤0.06–64	0.5	8	5
Ampicillin-sulbactam	≤0.06–256	1	8	0.5
Ticarcillin-clavulanate	≤0.06–256	0.5	8	0.5
Piperacillin-tazobactam	0.2–>256	4	16	0.5
Sanfetrinem[c]	≤0.06–256	0.1	1	
Quinupristin-dalfopristin[c]	≤0.06–2	0.5	1	
Trovafloxacin	≤0.06–8	0.2	1	1.8
Moxifloxacin[c]	≤0.06–32	0.5	2	
B. fragilis (133)				
Metronidazole	≤0.06–2	0.5	1	0
Chloramphenicol	0.1–4	2	4	0
Clindamycin	≤0.06–>256	0.5	>256	32.8
Cefoxitin	≤0.06–128	16	32	9
Ceftizoxime	≤0.06–>256	2	16	0.8
Cefminox	0.2–256	1	64	10.5
Cefotetan	≤0.06–>256	8	128	12
Piperacillin	≤0.06–>256	4	128	14.3
Imipenem	≤0.06–256	≤0.06	0.5	0.8
Meropenem	≤0.06–256	0.1	1	0.8
Amoxicillin-clavulanate	≤0.06–64	0.5	4	2.3
Ampicillin-sulbactam	≤0.06–256	0.5	4	0.8
Ticarcillin-clavulanate	≤0.06–256	0.2	4	0.8
Piperacillin-tazobactam	0.2–>256	1	16	0.8
Sanfetrinem	≤0.06–256	0.1	0.5	
Quinupristin-dalfopristin	0.1–2	0.5	1	
Trovafloxacin	≤0.06–8	0.2	1	1.5
Moxifloxacin	≤0.06–32	0.2	1	
B. thetaiotaomicron (39)				
Metronidazole	0.1–2	0.5	1	0
Chloramphenicol	2–8	4	8	0
Clindamycin	0.1–>256	2	>256	35.9
Cefoxitin	4–128	32	128	28.2
Ceftizoxime	1–>256	8	128	17.9
Cefminox	0.5–256	16	128	35.9
Cefotetan	4–>256	64	128	74.4
Piperacillin	2–>256	64	>256	43.6
Imipenem	≤0.06–1	0.2	1	0
Meropenem	≤0.06–4	0.2	2	0
Amoxicillin-clavulanate	0.1–32	2	8	5.1
Ampicillin-sulbactam	0.5–16	2	16	0
Ticarcillin-clavulanate	0.1–32	2	16	0
Piperacillin-tazobactam	1–32	16	16	0
Sanfetrinem	≤0.06–1	0.2	1	
Quinupristin-dalfopristin	≤0.06–2	0.5	2	
Trovafloxacin	≤0.06–8	0.5	2	0
Moxifloxacin	≤0.06–32	1	8	
B. uniformis (26)				
Metronidazole	0.1–2	0.5	1	0
Chloramphenicol	2–8	4	8	0
Clindamycin	0.1–>256	2	>256	38.5
Cefoxitin	0.2–32	8	32	0
Ceftizoxime	0.5–128	4	128	11.5
Cefminox	0.5–64	4	64	15.4
Cefotetan	0.5–128	32	128	46.2
Piperacillin	1–>256	16	>256	23.1
Imipenem	≤0.06–1	0.1	0.5	0
Meropenem	≤0.06–1	0.2	0.5	0
Amoxicillin-clavulanate	0.5–64	1	16	7.7
Ampicillin-sulbactam	0.5–16	1	8	0
Ticarcillin-clavulanate	≤0.06–16	1	16	0
Piperacillin-tazobactam	1–16	8	16	0
Sanfetrinem	≤0.06–1	0.1	1	
Quinupristin-dalfopristin	≤0.06–2	0.5	2	
Trovafloxacin	0.1–4	0.5	4	0
Moxifloxacin	0.1–32	1	8	
Imipenem-resistant *B. fragilis* (10)				
Metronidazole	0.25–2	0.5	2	0
Chloramphenicol	2–4	4	4	0
Clindamycin	0.25–>256	>256	>256	60
Cefoxitin	32–128	128	128	90
Ceftizoxime	64–>256	>256	>256	90
Cefminox	16–256	128	256	90
Cefotetan	32–>256	128	256	90
Piperacillin	32–>256	>256	>256	90
Imipenem	16–>256	256	>256	100
Meropenem	256–>256	256	>256	100
Amoxicillin-clavulanate	16–64	64	64	100
Ampicillin-sulbactam	32–>256	>256	>256	100
Ticarcillin-clavulanate	64–>256	>256	>256	100
Piperacillin-tazobactam	16–>256	>256	>256	90
Sanfetrinem	32–256	256	256	
Quinupristin-dalfopristin	0.2–1	0.5	1	
Trovafloxacin	0.1–4	0.2	2	0
Moxifloxacin	0.1–4	0.2	4	

[a] MICs are given in micrograms per milliliter.
[b] MICs (in micrograms per milliliter) from the NCCLS for resistant isolates are as follows: metronidazole and chloramphenicol, ≥32; clindamycin and trovafloxacin, ≥8; cefoxitin, cefminox, and cefotetan, ≥64; piperacillin and ceftizoxime, ≥128; imipenem and meropenem, ≥16; amoxicillin-clavulanate, ≥16-28; ampicillin-sulbactam, ≥32-16; ticarcillin-clavulanate, ≥128-2; piperacillin-tazobactam, ≥128-4.
[c] Breakpoints for sanfetrinem, moxifloxacin, and quinupristin-dalfopristin are not currently provided by the NCCLS for anaerobes.

tive against all of the imipenem-resistant isolates tested. Six of these strains were also highly resistant to clindamycin. Trovafloxacin and moxifloxacin showed excellent activity against imipenem-resistant strains. Quinupristin-dalfopristin inhibited these strains at a concentration of ≤1 μg/ml, while sanfetrinem yielded high MICs (range, 32 to 256 μg/ml).

In general, with the old antibiotics, our results are similar to those found in other studies in Spain (6, 12) and other countries (1, 10, 13, 18, 19). Resistance to the carbapenems and β-lactam–β-lactamase inhibitor combinations has been detected in our hospital since 1989 but with a very low incidence (0.5 to 1.5%). Several researchers have reported low rates of resistance to imipenem (1, 10, 18, 20). By comparing the results of this study with those of previous susceptibility studies reported by our group for isolates recovered between 1979 and 1995 (7, 8), we found that there were no significant changes in the overall susceptibility patterns during the last 5 years.

Our results confirm the previous finding that quinupristin-

dalfopristin has good in vitro activity against *B. fragilis* group organisms (16), although the quinupristin-dalfopristin MICs we obtained were slightly lower than those reported by Appelbaum et al. (3). Sanfetrinem appears to have excellent activity against *B. fragilis* group bacteria, as described previously by Di Modugno et al. (9) for *B. fragilis* strains. Our study shows high activity of trovafloxacin and moxifloxaxcin against *B. fragilis* group isolates, including those resistant to imipenem. Other studies (17, 20) have yielded values similar to ours for trovafloxacin. Several investigators (2, 11, 14) have also reported excellent activity of moxifloxacin against the *B. fragilis* group-.Moxifloxacin and trovafloxacin MICs for *B. fragilis* strains were lower than those seen for *B. thetaiotaomicron* and *B. uniformis* strains, as reported elsewhere (2, 17, 20).

There are geographic variations and changes over time in the susceptibilities of *B. fragilis* group organisms to different antimicrobials. The increased incidence among *B. fragilis* group bacteria to some antimicrobial agents, such as clindamycin or cephamycins, and the emergence of resistance to imipenem and β-lactam–β-lactamase inhibitor combinations require periodic susceptibility studies and the development of new broad-spectrum drugs. Given the excellent in vitro activity of trovafloxacin and moxifloxacin and their broad spectrum of activity, we suggest that both of them be considered as single agents in the treatment and prophylaxis of mixed aerobic-anaerobic infections involving *B. fragilis* group organisms. This study also confirms the excellent in vitro activity of sanfetrinem and quinupristin-dalfopristin against the *B. fragilis* group. Both the quinolones tested and the new streptogramin may play a potential role in the treatment of infections caused by imipenem-resistant *B. fragilis* strains and would also be a therapeutic option for patients allergic to β-lactams. Clinical studies will determine the therapeutic efficacy of the new agents tested. As it is not known whether resistant strains will emerge during therapy, *B. fragilis* group bacteria should be periodically monitored for the emergence of resistance to these new drugs.

REFERENCES

1. **Aldridge, K. E., M. Gelfand, L. B. Reller, L. W. Ayers, C. L. Pierson, F. Schoenknecht, R. C. Tilton, J. Wilkins, A. Henderberg, D. D. Schiro, M. Johnson, A. Janney, and C. V. Sanders.** 1994. A five-year multicenter study of the susceptibility of the *Bacteroides fragilis* group isolates to cephalosporins, cephamycins, penicillins, clindamycin and metronidazole in the United States. Diagn. Microbiol. Infect. Dis. **18:**235–241.
2. **Aldridge, K. E., and D. S. Ashcraft.** 1997. Comparison of the in vitro activities of Bay-128039, a new quinolone, and other antimicrobials against clinically important anaerobes. Antimicrob. Agents Chemother. **41:**709–711.
3. **Appelbaum, P. C., S. K. Spangler, and M. R. Jacobs.** 1993. Susceptibility of 539 Gram-positive and Gram-negative anaerobes to new agents, including RP59500, biapenem, trospectomycin and piperacillin/tazobactam. J. Antimicrob. Chemother. **32:**223–231.
4. **Babini, G. S., M. Yuan, and D. M. Livermore.** 1998. Interactions of β-lactamases with sanfetrinem (GV 104326) compared to those with imipenem and with oral β-lactams. Antimicrob. Agents Chemother. **42:**1168–1175.
5. **Bandoh, K., K. Ueno, K. Watanabe, and N. Kato.** 1993. Susceptibility patterns and resistance to imipenem in the *Bacteroides fragilis* group species in Japan: a 4-year study. Clin. Infect. Dis. **16**(Suppl. 4)**:**S382–S386.
6. **Baquero, F., and M. Reig.** 1992. Resistance of anaerobic bacteria to antimicrobial agents in Spain. Eur. J. Clin. Microbiol. Infect. Dis. **11:**1016–1020.
7. **Betriu, C., C. Cabronero, M. Gómez, and J. J. Picazo.** 1992. Changes in the susceptibility of *Bacteroides fragilis* group organisms to various antimicrobial agents 1979–1989. Eur. J. Clin. Microbiol. Infect. Dis. **11:**352–356.
8. **Betriu, C., A. Sánchez, M. Gómez, M. L. Palau, and J. J. Picazo.** 1999. In-vitro susceptibilities of the *Bacteroides fragilis* group to newer β-lactam agents. J. Antimicrob. Chemother. **43:**133–136.
9. **Di Modugno, E., R. Broggio, I. Erbetti, and J. Lowther.** 1997. In vitro and in vivo antibacterial activities of GV129606, a new broad-spectrum trinem. Antimicrob. Agents Chemother. **41:**2742–2748.
10. **Dubreuil, L.** 1996. *Bacteroides fragilis*: état de la sensibilité aux antibiotiques, évolution des résistances. Med. Mal. Infect. **26:**196–207.
11. **Edlund, C., S. Sabouri, and C. E. Nord.** 1998. Comparative in vitro activity of Bay 12-8039 and five other antimicrobial agents against anaerobic bacteria. Eur. J. Clin. Microbiol. Infect. Dis. **17:**193–195.
12. **García-Rodríguez, J. A., J. E. García-Sánchez, and J. L. Muñoz-Bellido.** 1995. Antimicrobial resistance in anaerobic bacteria: current situation. Anaerobe **1:**69–80.
13. **Hoellman, D. B., S. K. Spangler, M. R. Jacobs, and P. C. Appelbaum.** 1998. In vitro activities of cefminox against anaerobic bacteria compared with those of nine other compounds. Antimicrob. Agents Chemother. **42:**495–501.
14. **MacGowan, A. P., K. E. Bowker, H. A. Holt, M. Wootton, and D. S. Reeves.** 1997. Bay 12-8039, a new 8-methoxy-quinolone: comparative in-vitro activity with nine other antimicrobials against anaerobic bacteria. J. Antimicrob. Chemother. **40:**503–509.
15. **National Committee for Clinical laboratory Standards.** 1993. Methods for antimicrobial susceptibility testing of anaerobic bacteria, 3rd ed. Approved standard. NCCLS publication M11-A3. National Committee for Clinical Laboratory Standards, Villanova, Pa.
16. **Nord, C. E., A. Lindmark, and J. Persson.** 1989. Susceptibility of anaerobic bacteria to the new streptogramin RP 59500 in vitro. Eur. J. Clin. Microbiol. Infect. Dis. **8:**1064–1067.
17. **Snydman, D. R., and L. McDermott.** 1996. Analysis of the in vitro activity of trovafloxacin (CP-99,219) against *Bacteroides* species. Infect. Dis. Clin. Pract. **5**(Suppl. 3)**:**S96–S100.
18. **Snydman, D. R., L. McDermott, G. J. Cuchural, Jr, D. W. Hecht, P. B. Iannini, L. J. Harrell, S. G. Jenkins, J. P. O'Keefe, C. L. Pierson, J. D. Rihs, V. L. Yu, S. M. Finegold, and S. L. Gorbach.** 1996. Analysis of trends in antimicrobial resistance patterns among clinical isolates of *Bacteroides fragilis* group species from 1990 to 1994. Clin. Infect. Dis. **23**(Suppl. 1)**:**S54–S65.
19. **Turgeon, P., V. Turgeon, M. Gourdeau, J. Dubois, and F. Lamothe.** 1994. Longitudinal study of susceptibilities of the *Bacteroides fragilis* group to five antimicrobial agents in three medical centers. Antimicrob. Agents Chemother. **38:**2276–2279.
20. **Wexler, H. M., E. Molitoris, D. Molitoris, and S. M. Finegold.** 1996. In vitro activities of trovafloxacin against 557 strains of anaerobic bacteria. Antimicrob. Agents Chemother. **40:**2232–2235.