47th ICAAC,
Chicago 2007

F1-1644

Activity of Friulimicin B and Five Other Antimicrobial Agents against 179 Gram-Positive Obligatory Anaerobic Bacteria

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Revised Abstract

Background: Friulimicin B (FRI), an acidic cyclic lipopeptide, is intended for the treatment of severe infections caused by resistant Gram-positive pathogens. FRI shows structural similarities with daptomycin (DAP). We tested the activity of FRI compared with various other antimicrobials against 179 strains of Gram-positive obligately anaerobic bacteria.

Methods: FRI was compared with DAP, metronidazole (MET), moxifloxacin (MOX), linezolid (LIN) and vancomycin (VAN) against the following strains: *Clostridum difficile* (n=52), *Clostridium perfringens* (n=34), *Finegoldia magna* (n=14), *Peptostreptococcus* spp. (n=22), *Micromonas micros* (n=13), *Propionibacterium acnes* (n=19), *Lactobacillus* spp. (n=9), and *Eubacterium* spp. (n=16). MICs were determined employing the microdilution technique in Wilkens-Chalgren broth supplemented with vitamin K_1 and haemin. In addition, MICs of FRI were also determined by agar dilution accoding to CLSI standard M11-A6.

Results: While the broth microdilution yielded reproducible results, the activity of FRI in agar medium was more erratic. The MIC_{50} and MIC_{90} values for broth microdilution are listed in Table 1.

Conclusions: FRI has promising activity against several pathogenic species of anaerobes.

Introduction

Friulimicin B (FRI, Figure 1), an acidic cyclic lipopeptide, is intended for the treatment of severe infections caused by resistant Gram-positive pathogens[1-4]. FRI shows structural similarities to daptomycin, a lipodepsipeptide (DAP) but has been shown to have a different mode of action[5-6].

We tested the activity of FRI compared with various other antimicrobials against 179 strains of Gram-positive obligately anaerobic bacteria.

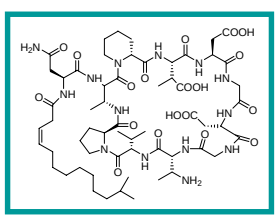


Figure 1 Friulimicin B

Methods

Bacterial Strains
179 Gram-positive anaerobes were taken from the culture collection from the Institute for Medical Microbiology and Epidemiology of Infectious Diseases, University of Leipzig, Germany. The strains were collected from clinical specimens at the Institute and from national and international studies and obtained in part from other laboratories. The following strains were used: *Clostridium difficile* (n=52), *C. perfringens* (n=34), *Finegoldia magna* (n=14), *Peptostreptococcus* spp. (n=22), (*P. anaerobius*, n=13; *P. asaccharolyticus*, n=6; *P. indolicus*, n=1; *P. prevotii*, n=2), *Micromonas micros* (n=13), *Propionibacterium acnes* (n=19), *Lactobacillus* spp. (n=9), (*L. acidophilus*, n=5; *L. casei*, n=2; *L. jensenii*, n=1; *Lactobacillus* spp. n=1), and *Eubacterium* spp. (n=16), (*E. aerofaciens*, n=5; *E. lentum*, n=9; *E. plautii*, n=1; *Eubacterium* spp. n=1). *S. aureus* ATCC 29213, *C. perfringens* ATCC 13124 and *E. lentum* ATCC 43055 were used as reference strains.

Antimicrobial Agents
Antimicrobial agents were obtained as laboratory powders of known potency from the manufacturers: FRI from Combinature Biopharm, Germany, DAP from Cubist Pharmaceuticals, Lexington, USA; metronidazole (MET) from Sigma Chemical Co., St. Louis, USA; moxifloxacin (MOX) from Bayer Vital GmbH, Leverkusen, Germany; linezolid (LIN) from Pharmacia & Upjohn Co., Kalamazoo, USA; and vancomycin (VAN) from Sigma Chemical Co., St. Louis, USA, respectively.

Broth microdilution MIC determinations
Tests were performed according to the recommendations of the Deutsches Institut für Normung (DIN) and standard DIN 58940-83[7]. The bacterial inocula were prepared by suspending growth from 24, 48 and 72 hour cultures grown on supplemented Columbia blood agar, respectively, (depending on the species) in Wilkins-Chalgren broth supplemented with vitamin K_1 and haemin. After semi-automated inoculation (Dynatech MIC-2000-inoculator, Dynatech Laboratories, Inc., Chantilly, USA) resulting in a final dilution of approximately 1.0×10^5 CFU/well (1.0×10^6 CFU/ml), plates were incubated for 48 h at 37°C in an anaerobic chamber. The MIC was defined as the lowest antibiotic concentration that inhibited visible growth. In addition, MICs of FRI were also determined by agar dilution according to CLSI standard M11-A6[8].

Results and Discussion

Organism (no. of strains tested)	FRI	DAP	MET	MOX	LIN	VAN
C. difficile (52)	0.125/0.25	0.25/1	0.125/0.5	1/16	0.5/2	0.5/1
C. perfringens (34)	1/2	0.5/2	2/4	0.5/1	2/2	1/1
F. magna (14)	0.25/1	0.5/1	0.5/4	0.125/2	2/2	0.25/0.5
Peptostreptococcus spp. (22)	0.25/1	0.25/1	0.25/1	0.125/1	1/1	0.5/0.5
M. micros (13)	1/2	0.5/2	0.25/>32	0.125/0.25	0.25/2	1/2
P. acnes (19)	1/2	1/2	>32/>32	0.25/0.25	0.5/1	1/1
Lactobacillus spp. (9)	2/4	2/8	>32/>32	1/2	4/8	4/>32
Eubacterium spp. (16)	8/>32	8/>32	1/32	0.5/2	4/32	4/16

Table 1 MIC_{50}/MIC_{90} (mg/L) of antimicrobials against anaerobes

Results and Discussion

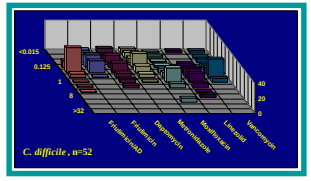
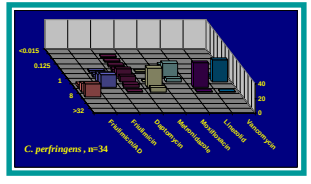


Figure 2



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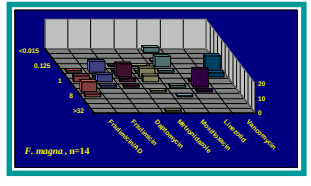

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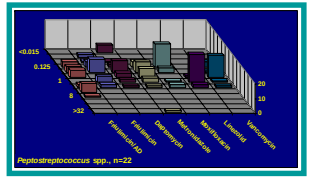

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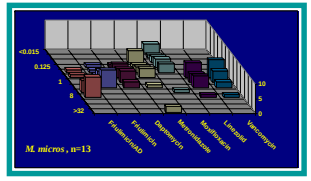

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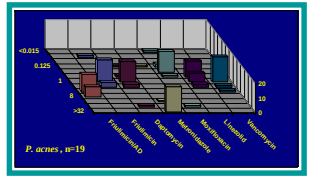

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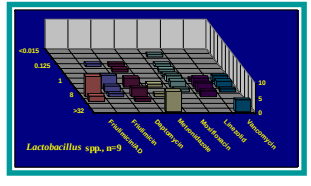

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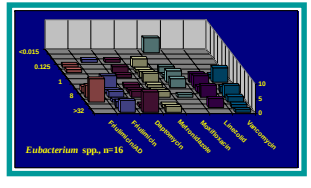

Figure 9

The figures 2-9 show the scatter histograms of MIC values obtained for FRI and the five other antimicrobial agents against 179 Gram-positive obligately anaerobic bacteria included in this study. The results obtained by testing in agar are indicated as Friulimicin/AD in each histogram.

FRI was particularly active against *C. difficile* (Figure 2), *F. magna* (Figure 4), and *Peptostreptococcus* species (Figure 5), where it was equal to or more active than DAP and metronidazole.

While results using the broth microdilution technique were reproducible, the activity of FRI in agar medium was more erratic.

Overall the *in-vitro* activity of FRI seems to be better than the *in-vitro* activity of DAP.

The MIC values against eubacteria (Figure 9) seem to display a bimodal distribution indicating that some strains are significantly less susceptible to FRI as well as to DAP.

Conclusions

- The novel lipopeptide friulimicin B has excellent activity against several pathogenic species of anaerobes.
- Friulimicin B has good activity against *C. difficile* and was more active than all 5 comparator drugs. *C. difficile* infections are now a major problem in many hospitals and institutions and friulimicin B could be a valuable agent for their treatment.
- Overall *in vitro* activity of friulimicin B compares favourably with that of daptomycin, metronidazole and moxi-floxacin.

Literature

[1] P. Bremer, et al., *AAC* 47 (2003) 3025-3029
[2] M. Kresken, et al., Poster F1-1642, this ICAAC 2007
[3] P. McGhee, et al., Poster F1-1648, this ICAAC 2007
[4] S. Schubert, et al., Poster F1-1644, this ICAAC 2007
[5] T. Schneider, et al., Poster F1-1640, this ICAAC 2007
[6] D. Zuehlke, et al., Poster F1-1643, this ICAAC 2007
[7] DIN, Deutsches Institut für Normung e.V. Medizinische Mikrobiologie und Immunologie: Diagnostische Verfahren. Berlin, Wien, Zürich: Beuth Verlag, 2004.
[8] Clinical and Laboratory Standards Institute (formerly NCCLS). Methods for antimicrobial susceptibility testing of anaerobic bacteria: Approved standard M11-A6. Wayne, PA, 2004