

Abstract 536 Gram Positive Isolates Associated with Skin and Skin Structure Infections (SSSIs) and Collected from Sites in the United States are Highly Susceptible to Retapamulin (SB275833), a Novel Topical Antimicrobial

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Abstract

Background: Retapamulin (formerly SB-275833) is a novel semi-synthetic pleuromutilin currently in development as a topical antimicrobial for the treatment of SSSIs. Pleuromutilins inhibit protein synthesis by binding to the 50S ribosomal subunits of bacteria and show no cross-resistance to other classes of antibiotics. Retapamulin is highly active against skin bacterial isolates carrying resistance determinants to established agents including β -lactams, macrolides, quinolones, fusidic acid and mupirocin. **Methods:** Clinical isolates of staphylococci, β -hemolytic and viridans streptococci were collected from 9 sites in the United States during 2004 and 2005. All isolates were collected and sent to the central laboratory for confirmation of identification and testing. Susceptibility testing was performed by the central laboratory using broth microdilution panels. Quality controls were performed each day of testing following Clinical and Laboratory Standards Institute (CLSI) guidelines. **Results:** MIC₅₀s (expressed in μ g/mL) were determined for retapamulin/mupirocin/neomycin/fusidic acid/bacitracin/erythromycin/tetracycline/linezolid/cephalothin/ceftriaxone/penicillin and amoxicillin/clavulanic acid against *Staphylococcus aureus* (n = 994): 0.12/8/64/1/1/128/32/16/4/16/64/32/16, respectively; coagulase-negative *Staphylococcus*, including *Staphylococcus epidermidis* (n = 297): 0.12/256/32/4/128/32/32/2/4/32/16/8, respectively; β -hemolytic (n = 1306): 0.06/1/64/8/128/4/32/1/0.25/0.12/0.12/0.25, respectively; and viridans streptococci (n = 304): 0.12/2/64/32/128/32/32/1/1/0.5/1, respectively. **Conclusions:** Retapamulin demonstrated greater activity against staphylococci, β -hemolytic and viridans streptococci isolates than commonly used topical and oral antimicrobial agents in the treatment of uncomplicated SSSIs.

Introduction

Gram positive bacteria are an increasingly common cause of community and hospital acquired infections, and their resistance to antibiotics is increasing. Retapamulin (SB-275833; Figure 1) is a novel, semi-synthetic derivative of the pleuromutilin class of antimicrobials and is currently in development for the topical treatment of Gram positive pathogens associated with secondarily infected traumatic lesions and dermatoses. Due to the unique pleuromutilin mode of action, retapamulin shows no target specific cross-resistance to other classes of antibacterial agents. The pleuromutilins are potent inhibitors of protein synthesis in bacteria presumably through the interference of peptide bond formation by binding to the peptidyl transferase center of the 50S ribosomal subunit.¹

Pleuromutilin derivatives have demonstrated significant *in vitro* activity against a variety of fastidious and non-fastidious veterinary and human bacterial pathogens especially methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci.² A comprehensive study was conducted to evaluate the *in vitro* activity of retapamulin and comparative antimicrobial agents against recently isolated clinical isolates of *S. aureus*, coagulase-negative staphylococci, *Streptococcus pyogenes*, *Streptococcus agalactiae* and viridans streptococci from skin and skin structure infections (SSSIs) during the course of a multi-center surveillance program in the USA.

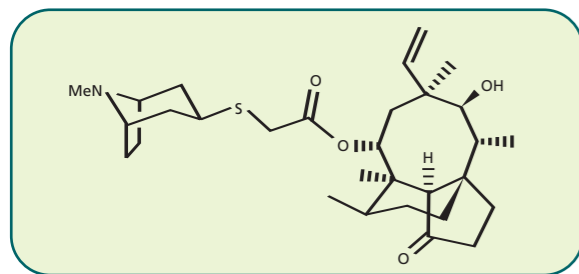


Figure 1. Chemical Structure of Retapamulin

Materials and Methods

- MIC endpoints were determined by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) guidelines³ for retapamulin and 14 comparators in customized dried broth microdilution panels (Trek Diagnostic Systems Ltd, West Sussex, UK). Comparator antimicrobial agents included: amoxicillin-clavulanic acid, bacitracin, ceftriaxone, cephalothin, clindamycin, cloxacillin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, penicillin and tetracycline.
- All study organisms were clinical isolates collected and frozen at -70°C from March 2004 to March 2005 from the USA. All isolates were obtained from SSSIs, primarily from infections seen in the community setting. Isolates were obtained from both adult and pediatric patients with one isolate per patient.
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as construction and management of a centralized database, were coordinated by International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).
- Mueller Hinton broth (Sensititre®, Cleveland, OH, USA) was used for all *Staphylococcus* species. Fresh lysed horse blood (Hemostat Laboratories, Dixon, CA, USA) was added to the Mueller Hinton broth to make the 3% lysed horse blood broth used for MIC testing of all *Streptococcus* species.
- The trays were incubated at 35°C in ambient air for 16 to 20 h before reading the MIC endpoints.
- Quality control testing was performed each day of testing as specified by the CLSI using the following ATCC strains: *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Streptococcus pneumoniae* ATCC 49619 and *Escherichia coli* ATCC 25922. In addition, quality control ranges previously determined for retapamulin were used as a control.⁴
- The total number of isolates, MIC₅₀ (μ g/mL), MIC₉₀ (μ g/mL) and MIC ranges were determined for all antimicrobial agents tested. Interpretive criteria and resistant phenotypes to the corresponding antimicrobial agent were defined according to CLSI breakpoints⁵ or the literature (mupirocin⁶ and fusidic acid only⁷).

Results

The results are listed in Tables 1–6.

Conclusions

- Retapamulin demonstrated excellent *in vitro* activity against all *S. aureus*, coagulase-negative staphylococci, *S. pyogenes*, *S. agalactiae* and viridans streptococci isolates tested in this study, including strains resistant to methicillin, erythromycin, mupirocin or fusidic acid.
- The *in vitro* activity of retapamulin (MIC₉₀) was 16- to 128-fold more active than fusidic acid, linezolid and mupirocin against all staphylococci and streptococci strains and equivalent to penicillin against all streptococci.
- Retapamulin inhibited all SSSI study strains from the USA with *in vitro* MIC values of \leq 0.5 μ g/mL against all isolates.

Table 1. List of 2905 Study Organisms from Skin and Skin Structure Pathogens in the USA

Organism/Phenotype	Breakpoints Used for Phenotypes (mg/mL) ^a	Study Counts
<i>S. aureus</i>		994
Methicillin-susceptible	Oxacillin \leq 2 μ g/mL	578
Methicillin-resistant	Oxacillin \geq 4 μ g/mL	416
Macrolide-susceptible	Erythromycin \leq 0.5 μ g/mL	295
Macrolide-intermediate	Erythromycin = 1–4 μ g/mL	69
Macrolide-resistant	Erythromycin \geq 8 μ g/mL	630
Mupirocin-susceptible	Mupirocin \leq 4 μ g/mL ^b	891
Mupirocin-resistant	Mupirocin \geq 8 μ g/mL ^b	103
Fusidic acid-susceptible	Fusidic acid \leq 1 μ g/mL ^c	949
Fusidic acid-resistant	Fusidic acid \geq 4 μ g/mL ^c	24
Coagulase-negative staphylococci		301
Methicillin-susceptible	Oxacillin \geq 18 mm	103
Methicillin-resistant	Oxacillin \leq 17 mm	198
Mupirocin-susceptible	Mupirocin \leq 4 μ g/mL ^b	164
Mupirocin-resistant	Mupirocin \geq 8 μ g/mL ^b	137
<i>S. pyogenes</i>		996
Macrolide-susceptible	Erythromycin \leq 0.25 μ g/mL	769
Macrolide-intermediate	Erythromycin = 0.5 μ g/mL	12
Macrolide-resistant	Erythromycin \geq 1 μ g/mL	215
Viridans streptococci		304
<i>S. agalactiae</i>		310
Total Isolates Tested		2905

^aPhenotypes are determined by the *in vitro* susceptibility of the respective antimicrobial agent against the corresponding organism as defined in CLSI document M100-S15 (2005) unless otherwise noted; ^bmacrolide = erythromycin activity; methicillin = oxacillin activity. ^cSusceptibility breakpoints as defined in Finlay *et al.*⁵

^dSusceptibility breakpoints as defined in Toma and Barriault.⁷

Table 4. MIC (μ g/mL) Summary Table for Retapamulin and Comparators against *S. pyogenes* from the USA (n = 996)

Compound ^a	%Sus	%Int	%Res	MIC (μ g/mL)		
				Range	MIC ₅₀	MIC ₉₀
Retapamulin	NA	NA	NA	0.008–0.12	0.03	0.06
Amox-Clav ^b	NA	NA	NA	\leq 0.015–0.5	\leq 0.015	0.12
Bacitracin	NA	NA	NA	0.25–128	2	32
Ceftriaxone	100	0	0	\leq 0.015–0.5	\leq 0.015	0.06
Cephalothin	NA	NA	NA	\leq 0.03–2	0.12	0.25
Clindamycin	97.7	1.2	1.1	\leq 0.015–32	0.03	0.12
Cloxacillin	NA	NA	NA	\leq 0.015–32	0.12	0.5
Erythromycin	77.2	1.2	21.6	\leq 0.015–32	0.03	2
Fusidic acid	NA	NA	NA	0.5–32	4	8
Gentamicin	NA	NA	NA	0.5–16	4	16
Linezolid	100	0	0	0.25–1	1	1
Mupirocin	NA	NA	NA	0.06–4	0.12	0.5
Neomycin	NA	NA	NA	4–64	32	64
Penicillin	100	0	0	\leq 0.015–0.12	\leq 0.015	0.03
Tetracycline	80.8	1.6	17.6	\leq 0.06–32	0.25	16

^aInterpretive criteria of compounds defined in CLSI document M100-S15 (2005), where available.⁵

^bAmoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration.

Sus, susceptible; Int, intermediate; Res, resistant; NA, not available.

Table 2. MIC (μ g/mL) Summary Table for Retapamulin and Comparators against *S. aureus* from the USA (n = 994)

Compound ^a	%Sus	%Int	%Res	MIC (μ g/mL)		
				Range	MIC ₅₀	MIC ₉₀
Retapamulin	NA	NA	NA	0.015–0.5	0.06	0.12
Amox-Clav ^b	55.8	0	44.2	0.12–32	2	16
Bacitracin	NA	NA	NA	4–128	>128	>128
Ceftriaxone	52.7	4.7	42.6	1–64	8	64
Cephalothin	57.7	0.3	42.0	0.12–256	1	16
Clindamycin	73.9	2.1	23.9	0.06–32	0.12	>32
Cloxacillin	NA	NA	NA	0.12–32	0.5	4
Erythromycin	29.7	6.9	63.4	0.12–32	32	>32
Fusidic acid	95.5	2.1	2.4	0.03–16	0.12	1
Gentamicin	93.8	2.8	3.4	\leq 0.03–64	0.25	2
Linezolid	100	0	0	0.5–4	2	4
Mupirocin	89.6	0	10.4	0.06–256	0.25	8
Neomycin	NA	NA	NA	0.06–64	2	64
Penicillin	5.9	0	94.1	\leq 0.015–32	8	32
Tetracycline	82.1	3.7	14.2	0.12–32	0.5	16

^aInterpretive criteria of compounds defined in CLSI document M100-S15 (2005), where available.⁵ Mupirocin susceptibility defined in Finlay *et al.*⁶ Fusidic acid susceptibility defined in Toma and Barriault.⁷ Note: β -lactams reported as resistant for MRSA in accordance with current CLSI guidelines.

^bAmoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration.

Sus, susceptible; Int, intermediate; Res, resistant; NA, not available.

Table 5. MIC (μ g/mL) Summary Table for Retapamulin and Comparators against Viridans Streptococci from the USA (n = 304)

Compound ^a	%Sus	%Int	%Res	MIC (μ g/mL)		
				Range	MIC ₅₀	MIC ₉₀
Retapamulin	NA	NA	NA	0.004–0.5	0.06	0.12
Amox-Clav ^b	NA	NA	NA	\leq 0.015–4	0.12	1
Bacitracin	NA	NA	NA	0.25–128	16	128
Ceftriaxone	92.8	3.0	4.3	\leq 0.015–16	0.12	1
Cephalothin	NA	NA	NA	\leq 0.03–32	0.5	1
Clindamycin	81.9	1.6	16.4	\leq 0.015–32	0.03	16
Cloxacillin	NA	NA	NA	0.03–32	2	8
Erythromycin	37.2	1.6	61.2	\leq 0.015–32	1	>32
Fusidic acid	NA	NA	NA	0.12–32	16	32
Gentamicin	NA	NA	NA	0.12–32	4	16
Linezolid	100	0	0	0.25–2	1	1
Mupirocin	NA	NA	NA	0.12–256	0.5	2
Neomycin	NA	NA	NA	0.12–64	32	64
Penicillin	61.8	36.8	1.3	\leq 0.015–8	0.12	0.5
Tetracycline	44.1	2.0	53.9	0.12–32	8	>32

^aInterpretive criteria of compounds defined in CLSI document M100-S15 (2005), where available.⁵

^bAmoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration.

Sus, susceptible; Int, intermediate; Res, resistant; NA, not available.

the agents commonly used in treatment, will provide a useful therapeutic option for such infections.

- Clinical trial data are needed to assess the clinical significance of these *in vitro* findings.

References

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Table 3. MIC (μ g/mL) Summary Table for Retapamulin and Comparators against Coagulase-negative Staphylococci from the USA (n = 301)

Compound ^a	%Sus	%Int	%Res	MIC (μ g/mL)		
				Range	MIC ₅₀	MIC ₉₀
Retapamulin	NA	NA	NA	0.008–0.5	0.06	0.12
Amox-Clav ^b	31.6	0	68.4	\leq 0.015–32	1	8
Bacitracin	NA	NA	NA	0.25–128	128	>128
Ceftriaxone	28.2	6.0	65.8	0.5–64	8	32
Cephalothin	34.2	0	65.8	0.06–64	1	4
Clindamycin	55.5	3.7	40.9	\leq 0.015–32	0.12	>32
Cloxacillin	NA	NA	NA	0.12–32	2	16
Erythromycin	21.3	2.7	76.1	\leq 0.015–32	>32	>32
Fusidic acid	83.7	2.7	13.6	0.03–32	0.12	4
Gentamicin	70.8	17.6	11.6	\leq 0.03–64	0.12	16
Linezolid	100	0	0	0.25–4	1	2
Mupirocin	54.5	0	45.5	0.06–256	1	>256
Neomycin	NA	NA	NA	\leq 0.03–64	1	32
Penicillin	11.6	0	88.4	0.015–32	2	16
Tetracycline	73.8	4.3	21.9	\leq 0.06–32	1	>32

^aInterpretive criteria of compounds defined in CLSI document M100-S15 (2005), where available.⁵ Mupirocin susceptibility defined in Finlay *et al.*⁶ Fusidic acid susceptibility defined in Toma and Barriault.⁷ Note: β -lactams reported as resistant for methicillin-resistant staphylococci in accordance with current CLSI guidelines.

^bAmoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration.

Sus, susceptible; Int, intermediate; Res, resistant; NA, not available.

Table 6. MIC (μ g/mL) Summary Table for Retapamulin and Comparators against *S. agalactiae* from the USA (n = 310)

Compound ^a	%Sus	%Int	%Res	MIC (μ g/mL)		
				Range	MIC ₅₀	MIC ₉₀
Retapamulin	NA	NA	NA	0.015–0.25	0.03	0.06
Amox-Clav ^b	NA	NA	NA	0.03–0.5	0.12	0.12
Bacitracin	NA	NA	NA	2–128	128	128
Ceftriaxone	99.7	0	0.3	0.03–1	0.06	0.12
Cephalothin	NA	NA	NA	0.12–2	0.25	0.5
Clindamycin	80.6	1.3	18.1	\leq 0.015–32	0.06	>32
Cloxacillin	NA	NA	NA	0.5–4	2	2
Erythromycin	54.5	1.6	43.9	\leq 0.015–32	0.12	>32
Fusidic acid	NA	NA	NA	0.5–32	8	16
Gentamicin	NA	NA	NA	1–64	16	32
Linezolid	100	0	0	0.5–2	1	1
Mupirocin	NA	NA	NA	0.25–8	1	1
Neomycin</						